RESEARCH COMMUNICATION

Familial Breast Cancer Registry Program in Patients Referred to the Cancer Institute of Iran

Tayebeh Sabokbar[1], Elias Khajeh[2], Foad Taghdiri[2], Vahideh Peyghambari[1], Reza Shirkoohi[1]*

Abstract

Introduction: Annually a considerable number of people die because of breast cancer, a common disease among women also in Iran. Identifying risk factors and susceptible people can lead to prevention or at least early diagnosis. Among susceptibility risks, 5-10% of patients have a family history predisposing factor which can influence the risk of incidence among the family. Having a registry program can be a more practical way to screen high risk families for preventive planning. Method: Based on inclusion criteria, a questionnaire was prepared and after a pilot study on a small number of patients, actual data were collected on 400 patients and processed in SPSS 16.0. Results: Totally, 28.2% of the patients were younger than 40 years old and 36.8% had the included criteria for familial breast cancer (FBC). 102 patient's samples could be compared for receptor presentation. Similar to other studies, the number of triple negative breast cancers increased as the age decreased. Conclusion: The high percentage of patients with FBC among 400 cases in this study demonstrates that in order to design an infrastructural diagnostic protocol and screening of patients with FBC, a precise survey related to frequency and founder mutations of FBC is needed nationwide.

Keywords: Breast cancer - familial breast cancer - screening - registry program

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Introduction

Breast cancer is one of the most common invasive cancers among women. It includes 22.9 percentage of invasive cancers in women and 16 percent of all cancers. In 2008, breast cancer was responsible for 458,503 number of global mortalities (13.7% cancer death in women and 6% in both genders) (World Cancer Report, 2011). Lung cancer was the second cause of cancer death including 12.8 percentage of mortality in women (18.2% of total mortality in both sexes) (World Cancer Report, 2011)

Global statistics indicate a significant increase of incidence based on modern life style, weight gain and physical activity decrement as a result of machine life. (Carmichael et al., 2009; World Health Organization, Breast cancer: prevention and control) Due to high incidence and mortality rate of breast cancer in women, consulting-therapeutic systems in different countries have become specified for treatment and prevention planning of this cancer in order to decrease the mortality rate. Hence, many studies have been conducted on the diagnosis, screening, prevention and treatment of breast cancer.

In our country, because of high incidence of breast cancer among women and the difference in distribution and dispersion of disease in different areas, recognition, prevention and treatment of this cancer should be one of the main priorities. Identifying the effective risks regarding breast cancer among Iranian women requires many works. Since there are differences between sporadic and familial cases, e.g. younger ages and worse prognosis in familial breast cancer (FBC), one of the prior necessary procedures for prevention is screening and diagnosis of breast cancer cases for reducing the mortality rate, separating familial cases from sporadic ones and finding their frequency. Also by identifying the familial cases and gaining more information about them, prospective projects could be designed for factors susceptible to the etiology like mutations and polymorphisms (Nordin et al., 2011).

It should be noted that differentiation of this category of breast cancer needs precise and integral history which is not taken by routine patient interview. By studying and establishing a defined registry system, we can overcome the difficulties and deficiencies of the patient's history making. Moreover, due to the different prevalence of this cancer on various races, environmental agents and different life styles in different areas of Iran, the definition of localized criteria for suitable screening will be necessary in the future. In fact the aim of this study was to find out the prevalence of FBC and the awareness of these cases conditions in Iran, establishing a screening and counseling system plus risk assessment and appropriate protocol for breast cancer patients.

*[1]Department of Genetics, Cancer Research Center, Cancer Institute of Iran, [2]Students Scientific Research Center & Exceptional Talent Development Center (ETDC), Tehran University of Medical Sciences (TUMS), Tehran, Iran *For correspondence: rshirkoohi@tums.ac.ir*

Table 1. Inclusion Criteria for FBC

1- Female breast cancer before the age of 40 years old
2- Breast cancer in proband within 40-50 and one MBC and one b/l breast cancer or ovarian cancer in the same blood line
3- Breast cancer and melanin spots on the lips or buccal mucosa
4- Breast cancer and oral papillomatosis and/or facial trichilemmomas
5- Multiple primary tumors (e.g. breast/ovary, breast/thyroid, breast/sarcoma, breast/breast)
6- Pancreatic cancer and a family history of breast cancer before age 50 (within three generations)
7- Early-onset prostate cancer (before age 55) and a family history of breast cancer before age 50 (within three generations)
8- A demonstrated germ line mutation in a high risk breast cancer associated gene such as BRCA1, BRCA2 and Tp53 by genetic tests
9- Cowden syndrome, Li-Fraumeni, Peutz-Jegher, ataxia-telengiectasia
10- ≥4 breast cancer within first degree relatives
11- One or more first or second degree relatives diagnosed with breast cancer before the age of 50
12- Two first or second degree relatives on the same side of family diagnosed with breast or ovarian cancer
13- One or more first or second degree relatives with male breast cancer
14- One or more first or second degree relatives with bilateral breast cancer
15- One or more first or second degree relatives with breast and ovarian cancer
16- Two or more first or second degree relatives with breast cancer average age ≤49
17- One or more second degree relatives with breast cancer ≤40 +first or second degree relatives with childhood malignancy
18- One second degree relative diagnosed with breast cancer at age ≤45 + another first or second degree relative on the same side of the family with bone or soft tissue sarcoma at age ≤45
19- Several generation of people with the same or related cancers (autosomal dominant patterns)

Materials and Methods

A criteria list was prepared according to standardized criteria of different countries. 67 patients who had referred to our cancer institute were interviewed as the pilot study. The aim of this pilot study was to evaluate the practical usage of the questionnaire and to estimate FBC prevalence.

After necessary modifications in questionnaire, the final study was performed on 400 patients who had referred to our Cancer Institute from January 2010 to November 2011. All demographic information, clinical and pathology data, and family history were recorded. The patients were informed about the aim of the study prior to their enrollment and written consent was taken from them. Data elicitation was recorded in MS Excel 2010.After the primary analysis, the rest of the work was conducted with SPSS 16.0 (SPSS Inc., Chicago 11). Including criteria for hereditary cancer has been given in Table 1.

Table 2. Demographic Data

Variable	N	%	p value (CI)
Age of Patient			
<40	99	24.8	1.752
>40	300	75	(1.71-1.79)
Missing	1	0.2	
Age of Patient when Diagnosed			
<40	113	28.2	1.713
>40	284	71	(1.67-1.76)
Missing	3	0.8	
Gender			
Female	398	99.5	1.005
Male	2	0.5	(1.00-1.01)
Marriage Status			
Single	27	6.8	1.962
Married	364	91	(1.93-2.00)
Missing	9	2.2	
Occupational Status			
Housewife	319	79.8	1.58
Working	81	20.2	(1.41-1.75)
Education level			
Uneducated	60	15	3.685
Primary School	97	24.2	(3.45-3.92)
Secondary School	71	17.8	
Diploma	77	19.2	
University	34	8.4	
Missing	61	15.2	

Results

A total number of 400 patients entered this study from which 99 cases (24.8%) were under 40 years old and 300 cases (75.0%) were more than 40 years old (0.2%had not given information about this variable). The age distributions based on time of diagnosis for the two groups were 28.2 and 71.0 percentages respectively (0.8% missing). Maximum age was 83 and minimum was 19 years old with the average age of 47. The dominant gender was female (398 cases 99.5%) and only 2 cases (0.5%) were male. Majority (90.0%) were married and

Table 3. Disease Condition and Associated Diseases

Variable	N	%	p Value (CI)
Breast Involvement			
Unilateral	373	93.2	1.068
Bilateral	19	4.8	(1.04-1.10)
Primary Bilateral	4	1	
Missing	4	1	
Primary tumor			
Not Associated	384	96	1.038
Associated	15	3.8	(1.02-1.06)
Missing	1	0.2	

Table 4. Family History of Cancer

Variable	One Person		Two Persons		Three or More		Without History		Missing		p Value (CI)
	N	%	N	%	N	%	N	%	N	%	
First Degree Relatives	70	17.5	8	2	5	1.2	303	75.8	12	3	4.966 (4.77-5.16)
Second Degree Relatives	55	13.8	16	4	3	0.8	308	77	17	4.2	5.086 (4.90-5.27)
Third Degree Relatives	42	10.5	7	1.8	2	0.5	330	82.5	19	4.8	5.36 (5.19-5.52)

only 6.8% were single (2.2% missing). Occupational status revealed that 79.8% were housewife. Assessment of educational levels demonstrated that 15.0% (60 cases) were uneducated, 24.2% (97 cases) had primary education, 17.8% (71 cases) had secondary school education, 19.2% (77 cases) had high school education and 8.4% (34 cases) had university degrees (15.2% missing). All demographic data are shown in Table 2.

In general, patients were referred to our center from 24 different provinces and the maximum number of referrals were from Tehran Province with 142 cases (35.5%) followed by Lorestan Province with 36 cases (9.0%). About 93.2% had unilateral involvement of breast cancer while 1.0% had primary bilateral breast cancer (Table 3). Fifteen cases (3.8%) had a history of another primary tumor (Table 4) which was mostly thyroid cancer (7 cases).

A total number of 102 patients had information about estrogen receptor (ER) from which 71 and 31 cases were positive and negative, respectively. Also, the number of progesterone receptor (PR) was positive and negative in 64 (62.7%) and 38 (37.3%) of the cases, respectively. Regarding human epidermal growth receptor 2 (HER2), 34 (33.7%) of all cases were positive and 67 (66.3%) were negative. In case of the distribution of ER, PR and HER2 presentation and first degree relative history of cancer, there was no significance difference between patients with positive and negative history of a family member with cancer (Table 5). There were no significance differences regarding the age of diagnosis and receptor presentation. The logistic regression has shown that there is an increased risk of incidence of triple negative disease with age decrement (OR: 3.10, CI: 1.00-9.60) (Table3).

In relation to the family history background of cancer, 20.7% (85 cases) had one or more first relatives with cancer history, from which 7.0% (28 cases) had related or the same cancer (ovary, breast). These statistics for second and third relatives were 18.8% (75 cases) and 12.8% (49 cases) and as for related cancer they were 3.25% (13 cases) and 5.7% (23 cases) respectively (Table 4). It was demonstrated that 147 cases (36.8%) had the criteria for familial cancer and were diagnosed as FBC (Figure 1).

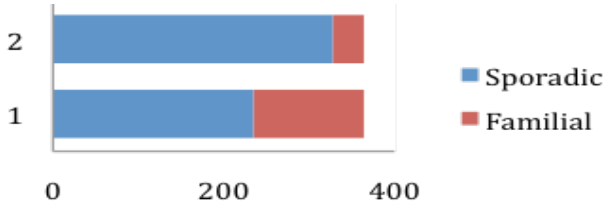

Figure 1. FBC Frequency is Higher in Cancer Institute Patients Compared with Global Estimation

Table 4. Tumor Marker Characteristics and Age of Diagnosis

Variable	Age at Diagnosis				Risk (OR (CI))
	<40 years		>40 Years		
	N	%	N	%	
ER Positive	17	60.7	53	72.6	NS*
ER Negative	11	39.3	20	27.4	
PR Positive	16	57.1	47	64.4	NS*
PR Negative	12	42.9	26	35.6	
Her2 Positive	6	21.4	27	37.5	NS*
Her2 Negative	22	78.6	45	62.5	
TNBC	7	26.9	8	10.7	OR: 3.10 (CI: 1.00-9.60)
At least One is positive	19	73.1	67	89.3	

*NS Not Significant

Discussion

In year 2000, it was estimated that one million new cases of breast cancer are added to the world annually. In United States the estimated number was 226,870 new cases for female and 2,190 for male breast cancer from which 39,510 of female and 410 of male breast cancers resulted in death in 2012 ("American Cancer Society.: Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society, 2012"). A study in Spain has revealed that 13,500 new cases of breast cancer are added annually from which 1,350 of them have familial history (Monge et al., 2004). A study which was conducted in Iran in 2004 demonstrated that the higher incidence ages were in the range of 45-65 and more than 80 years old (The Ministry of Health Treatment and Medical Education, 2004).

Breast cancer has a strong correlation with age. While statistics have shown that only 5% of patients are younger than 40 years old (Vogel et al., 2011), age distribution of our study has revealed a significant decrease in the age of patients being referred to our institute. A conducted study in Tehran has demonstrated that 31.4% of breast cancer tumors occur in patients younger than 40 years old (Mousavi et al., 2006). Our data also indicate that the level of knowledge should be raised especially in lower social and educational conditions. It is likely that increase of educational level followed by awareness about cancer can lead to early detection and treatment of the disease (Hussain et al., 2008; Hajian et al., 2011).

A family history of a characterized cancer especially ovary, breast, colorectal and prostate could increase the risk of incidence in the other members of the family. By recording a three generation pedigree, high risk members of the family could be recognized so that with follow up and an appropriate life style, the risk of incidence could be decreased relatively (Eccles et al., 2000; Eberl et al., 2005).

Generally about 5-10% of breast, ovary and colorectal cancers are hereditary (Anand et al., 2008). The required information could not be collected in routine medical investigations and it is probable that such patients and their families would not be investigated for risk of cancer and no prophylactic effort would be done for them (Katki, 2006). In many organized cancer centers, a patient refers to the familial cancer clinic and is informed about risk and mutation inheritance. Also, there will be some advices for decreasing the risk and information will be given on early detection and genetic tests (Stewart, 2001). Moreover, other than genetic and screening investigations, periodic clinical and Para-clinical exam for early detection will be performed for such patients (Warner et al., 1999; Stewart, 2001; Minceym, 2003).

At least there are 40 genes that are related to breast cancer which two of them are with high penetration (BRCA1&2) and the rest are with low penetration. Therefore, FBC is a polygenic disease (Yeo et al., 1996;

Peto et al., 1999; Goldgar, 2002; Jonker et al., 2003; Ropka, et al., 2006; Slijepčević, 2007). In other cases it is associated with well-known syndromes (Seal et al., 2003). Cancer tumor characteristic markers could be a clue for investigating gene involvement.

For instance the frequency of BRCA mutation is higher in early onset triple negative breast cancer (TNBC) cases (Lee, 2008; Young et al., 2009; Bouwman et al., 2010; Fostira et al., 2012). TNBC is a more invasive cancer with higher degree of recurrence. About 14 to 20 percentages of breast cancers are triple negative (Carey et al., 2006; Hannemann et al., 2006; Lund et al., 2010). Similar to our study, the significant increase of the triple negative tumors with decrease of cancer onset age has been shown in many other studies in different countries that TNBC has been more frequent in younger ages (Dobi et al., 2011; Salami et al., 2011).

Studies have shown that the incidence age of breast cancer in Iran is at least a decade less than the developed countries (Harirchi et al., 2000; Harirchi et al., 2004). This clarifies a critical demand to investigate genetic predisposition factors in this country. Although valuable studies regarding to breast cancer germ line mutations have been done in Iran (Ghaderi et al., 2001; Ghaderi et al., 2001; Yassaee et al., 2002; Moslehi et al., 2003; Pietschmann et al., 2005; Khadang et al., 2007; Ohadi et al., 2007), more unanswered questions still remain.

In conclusion, as a final conclusion, high percentages of patients with FBC among 400 cases of this study have demonstrated that in order to design an infrastructural diagnostic protocol and screening of patients with FBC, a precise survey related to frequency and founder mutations of FBC is needed nationwide.

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