RESEARCH COMMUNICATION

Laddering Through Pedigrees: Family History of Malignancies in Primary Breast Cancer Patients

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Abstract

A family history (FH) of breast cancer (BC) is a long recognized risk factor for developing the disease. Also, there have been some reports of links between an FH and some other malignancies (mostly uterus, ovary, and prostate cancers), and an increased risk of developing BC. In this paper we present descriptive report of the occurrence pattern of malignancies in families of BC afflicted patients through 4 generations. Patients included 542 Iranian primary BC cases, presenting at an outpatient clinic for treatment and follow-up. Detailed pedigrees were drawn for each patient, and data for a total of 6220 relatives were gathered. Among the probands, 29.9% and 53.9% had a positive FH of BC and other malignancies (OM) respectively. Mean number of breast cancers was nearly double in maternal-lines versus paternal-line relatives. Also, occurrence of brain, uterus, and colorectal cancers was significantly higher in maternal-line relatives, but conversely, liver cancer showed a tendency toward paternal-line relatives (1st degree relatives excluded). The highest frequency of BC involvement was noted in 2nd degree/2nd generation, and 3rd degree/3rd generation relatives. For OMs, although gastric cancer was by far the most frequent OM across pedigrees, uterus cancer, and hematopoeitic system lesions (leukemia) predominated over gastric cancer through the 3rd and 4th generations respectively. We did not find any relation between having a positive FH of BC, and developing early-onset BC. The findings discussed in this paper were partially presented at the 18th UICC International Cancer Congress, Oslo-Norway, 30 June-5 July 2002.

Key Word: Pedigree - family history - breast cancer - other malignancies - Iran

Introduction

Breast cancer (BC) is a leading women's health paradigm with a considerable burden (Alberg and Helzlsouer, 1997) and a family history (FH) of BC in close relatives is a well known risk factor for the disease (Kelsey and Gammon, 1990). Cancer involvement of several members of some families is an established fact, dating back to at least the 1800s (Newman et al., 1997; Broca, 1866), but the first empiric demonstration that women with an FH of BC are more likely to become afflicted with the disease and eventually die from it was not published until 70 years ago (Lane-Claypon, 1926). Since then, an ever-increasing body of evidence has put forward FH of the BC as one of the most consistently documented risk factors of the disease (Newman et al., 1997). Across all ages, women with BC are, on average, 2 to 3 times more likely to have an FH of the disease in a 1st-degree relative than controls (Kelsey,1979; Kelsey and Gammon, 1990; Eby et al.,1994). This may be

due partly to the fact that relatives tend to be exposed to the same environmental risk factors, but also an inheritable (genetic) susceptibility might be involved (Houlston and Peto, 1996).

Although FH has long been recognized as the principal risk factor in BC, high numbers of different afflicted relatives are only observed in rare families, and many patients are found to have no close affected relative (Margaritte-Jeannin et al.,1995). All in all, segregation analysis has revealed a mixed nature for BC, in which approximately 5% to 10% of cases are regarded as inherited cases, and remaining, as sporadic cases (Bishop et al.,1988; Claus et al.,1991; Kelsell et al.,1993; Newman et al., 1988; Williams and Anderson, 1984). The statement of familial aggregation comes from descriptive studies of large extended pedigrees containing multiple family members with BC alone, or in conjunction with other cancers (Anderson, 1974; Lynch et al., 1974).

There are some factors which are believed to be linked to this familial segregation of BC. For example, age at onset

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of BC in relatives and whether the relative affected is the mother and/or sister(s) may give rise to different BC risks (Peto, 1980).

The age of onset is believed to be varied among inherited and sporadic cases. The incidence of BC increases with increasing age and is believed to be relatively rare below the age of 40 years. Data from genetic epidemiology studies of BC are likely to be deficient in numbers of early-onset cases (Eccles et al., 1994), but familial BCs generally strike at a much earlier age (Margaritte-Jeannin et al.,1995). Also, the risk of BC in 1st degree relatives is greatest with those with an FH of BC with an early age of onset (Ottman et al., 1986; Claus et al., 1990). Some other studies have found that an FH of BC is a stronger risk factor at younger proband age (Claus et al., 1990; Brinton et al., 1982; Calle et al.,1993), although the evidence is not consistent (Colditz et al., 1993; Parazzini et al., 1993; Peto et al., 1996, Atri et al., 2003). We have found a lack of any association between early onset of breast cancer and numbers of affected relatives in an Iranian population (Atri et al., 2003).

The association between BC and an FH of the disease is generally stronger considering women with bilateral disease (Newman et al., 1997; Ottman et al., 1986; Slattery and Kerber, 1993; Tulinius et al., 1992; Byrne et al., 1991), together with the above-mentioned earlier onset of disease (measured either by age or menopausal status at diagnosis) (Ottman et al., 1986; Claus et al., 1990; Colditz et al., 1993; Slattery and Kerber, 1993; Tulinius et al., 1992; Schwartz et al., 1985). Moreover, when FH includes more distant relatives (e.g. 2nd or 3rd degree), the association is usually weaker (Slattery and Kerber, 1993; Tulinius et al., 1992; Byrne et al., 1991; Schwartz et al., 1985), and when it includes more than one 1st-degree relative with BC, the association becomes stronger still (Claus et al., 1990; Tulinius et al., 1992; Byrne et al., 1991; Schwartz et al., 1985).

Slightly higher relative risks (3 to 4) are also reported for ovarian cancer in families with a history of BC (Amos and Struewing, 1993). Further more, FH of colon, prostate, ovarian and other cancers including gynecological cancers has been associated with an increased risk of BC in some but not all studies (Peto, 1980; Parazzini et al., 1993; Thompson and Schildkraut, 1990; Anderson et al., 1992; Tulinius et al., 1992; Anderson and Badzioch, 1993; Goldgar et al., 1994; Teare et al., 1994).

Most research has been conducted in North America and north European countries. The familial predisposition to BC however may have different genetic and environmental correlation in different populations including the prevalence of various susceptibility genes and the impact of various environmental factors (Negri et al., 1997).

In a previous report (Negri et al., 1997), regarding the relation between FH of cancer in first degree relatives and the risk of BC on the basis of large case-control study, 2569 BC afflicted women with the age ranging from 23 to 74 (with mean of 55) were analyzed.

A significant increase in BC was observed with an FH

of intestinal (OR 1.32) and BC (OR 2.38). Seven cases and one control reported a history of gallbladder cancer in first-degree relatives (OR 8.57). FH of other cancers was not related to BC risk, although a not very significant correlation was noted for ovary (OR 1.29), kidney (1.70), lymphoma (1.71) and leukemia (1.35) (Negri et al., 1997). The OR of BC with reference to FH of BC in different strata of the age of the probands and other selected co-variants was compared. No trend with age at diagnosis was evident and the highest OR was noted at age 60 or over, followed by group below 45 years (Negri et al., 1997).

The OR of BC according to the type of relative with history of BC and the age of the relative was also considered. Compared with women with no history of BC in first-degree relatives, those with only the mother affected had an OR of 2.26, those with only sister had an OR of 2.56, and those with both the mother and sister affected had an OR of 2.36. Relative to women with no first-degree relatives with BC, those with a first-degree relative with BC diagnosed below age 40 had an OR of 3.51, while those with relatives with BC diagnosed above age of 40 had an OR of 2.17 (Negri et al., 1997).

The mortality in mothers and sisters for specific causes of death is presented in a report of 740 index cases of BC and their pedigrees. There was no marked overall excess mortality for cancers other than BC (51 death, significant mortality ratio (SMR) 1.26, p=0.13) although there was stronger evidence of an excess below age 50 (20 death, SMR 2.01. p=0.007). Cancers of the cervix, endometrial, and lung were all significantly elevated below age 50 (SMRs 3.47, 10.53, and 5.88 respectively) (Anderson et al., 1992). This study showed 70 BC cases among 1568 mothers and sisters (a frequency of 0.0446) (Anderson et al., 1992).

The observed excess of lung cancer and uterine cancer which were particularly below age 50 were somewhat surprising (Schildkraut et al., 1989).

Excess of endometrial cancer is reported in relatives of BC cases diagnosed under age of 40 (Peto et al., 1996). However in the same study, no excess of lung cancer or cervical cancer among the BC relatives was observed.

Most of the pedigree information is obtained on the basis of probands' claims, although cases may have been confirmed by hospital records, or death certificates (Anderson et al., 1992). The more extensive the FH, the greater certainly will be about the carrier status. This is well illustrated by the family studies in previous reports (Margaritte-Jeannin et al.,1995). Also, it has been suggested that age of onset provides limited information on the carrier status of affected individuals and most be used with caution in genetic counseling (Margaritte-Jeannin et al.,1995).

In most of the studies, the pedigrees are confined to first-degree and at most, second-degree relatives. But in Iran, close relationship among family members enables us to rely more on the information about more distant relatives (3rd and 4th degree relatives, e.g. first, second and even third cousin). Thus Iranian family members are usually well aware of familial events, including diseases, births and deaths.

Table 1. Total Studied Relatives. (Bold numbers indicate patients themselves.)

	1st Generation	2nd Generation	3rd Generation	4th Generation	5th Generation	Total
Male	248	668	1121+6	793	68	2898+6
Female	267	734	1423+536	835	63	3322+536
Total	515	1402	2544+542	1628	131	6220+542

Patients & Methods

Cases included 542 Iranian primary BC patients, diagnosed between 1994 and 1999. They didn't have any history of a previous malignancy and they all received standard treatment. Patients with stage 4 disease were excluded to minimize possible interference between patients' disease course and obtaining family history data.

Patients and their accompanying relatives were initially interviewed by our geneticist to draw the basic pedigrees. Subsequently, further interviews with patients and their relatives were constructed to increase the details and reliability of the pedigrees.

The pedigrees were drawn upon patients' and their relatives' claims, but whenever possible, medical documents and reports were used to substantiate these claims.

Data regarding patients' characteristics, their familial history, and type, age at diagnosis, degree, parental line, and generation of cancer afflicted relatives were extracted from the pedigrees and entered to SPSS (version 10) program to construct the database, which was subsequently analyzed. Probands' generation was considered as 3rd generation. Analysis was performed with both inclusion and exclusion of the probands. Whenever cited, ranges are mean±2SE.

Results

In order to investigate the different cancer involvement patterns among the breast cancer (BC) afflicted patients' blood relatives, and to reveal the possible relations, we analyzed a comprehensive database of 542 BC patients' families with emphasis on the breast and other frequent malignancies (OM) and their occurrence according to the different generations, degrees, and parental lines. Probands were put in the 3rd (Figure 1) generation.

The mean age of the patients was 48.9±0.97. Of these patients, 29.9 and 53.9% had a positive FH of breast and other malignancies respectively. Data was available for a total of 6220 blood relatives (Table 1).

A total of 213 BC cases were reported in these families (542 probands excluded) with the maximum of 4 BC cases in individual families. Frequencies and standardized ratios are showed in Table 2.

These cases were observed across 1st to 4th generations and among 1st to 4th degree relatives (Table 3). Breast cancer occurrences in first, second and third generation and in first, second and third degree relatives were associated (P< 0.001). Mean number of breast cancers was nearly double in maternal-lines versus paternal-line (0.17 vs. 0.09, P= 0.002) (First degree relatives excluded).

Considering the OM's, a total of 477 cases were reported in the families, with the gastric (63), lung (49), uterus (44), hematopoeitic system (40), brain (34), colorectal (30), esophagus (28), prostate (28), liver (25), and lymphoid tissue (23) cancers as the leading malignancies. Frequencies and standardized ratios are showed in Table 4.

The mean age of the BC afflicted relatives in 1st, 2nd, 3rd, 4th and all generations at the time of diagnosis was 55, 51.92, 41.14, 41.95, and 47.14 years old respectively.

Of the BC afflicted relatives, 121, 50, 32, and 8 cases belonged to the maternal, paternal, sister and brother lines respectively, and the 1st degree relatives in these lines (i.e. mother, father, sister, and brother) consisted of 28, 1, 33, and 0 cases respectively.

Considering the OMs, gastric, lung, uterus, hematopoeitic system, brain, colorectal, esophagus, prostate, liver, lymphoid tissue (Lymphoma), and ovary cancers were selected. The number of cases according to parental line is showed in Table 5.

The distribution of relatives' OMs and frequencies of different malignancies across 1st, 2nd, 3rd, 4th, and all generations are presented in table 6.

Of all the OM afflicted relatives, 93, 103, 75, and 5 cases belonged to the 1st, 2nd, 3rd, and 4th degree relatives. The
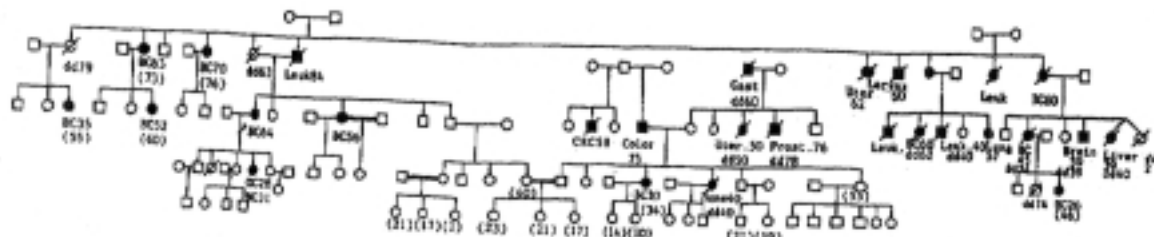

Figure 1.A sample pedigree.

Figure 1. Patient Pedigrees

Table 2. Frequency of BC According to Sex and Generation. (Numbers in parentheses indicate ratios with probands included.)

	Total No. of Cases	Standardized Ratios		
		No. of Cases to Total Male Relatives*	No. of Cases to Total Female Relatives*	No. of Cases to Total Relatives*
1st Generation	21	0.085	0.079	0.041
2nd Generation	90	0.135	0.123	0.064
3rd Generation	81 (623)	0.072 (0.553)	0.057 (0.318)	0.032 (0.092)
4th Generation	21	0.026	0.025	0.013
5th Generation	0	0	0	0
All	213 (755)	0.073 (0.260)	0.064 (0.196)	0.034 (0.112)

* In the same generation.

distribution of cancers among different relatives is presented in table 7.

We also took a look at the age of cancer afflicted relatives in different generations. In order to take probands' age and its possible effects as a general risk factor of cancer development into account, distribution of malignancies were compared according to probands' age. Considering the OMs, the mean age of the FH(+) and FH(-) probands was 49.70 and 48.43 (Mean difference 1.2709, 95% CI of the difference -.6925 to 3.2343). The mean age of the probands according to each type of cancers is presented in table 8.

Discussion

A positive family history (FH) of Breast Cancer (BC) is noted in approximately 20-30 % of the BC afflicted patients

Table 3. Frequency of BC Among Relatives and Across Generations.

	1st Gen.	2nd Gen.	3rd Gen.	4th Gen.	Total
1st Degree	-	28	32	8	68
2nd Degree	5	49	6	7	67
3rd Degree	16	13	40	4	73
4th Degree	0	0	3	2	5
Total	21	90	81	21	213

in general studies. The importance of FH as a risk factor (and as showed by the authors elsewhere, a possible prognostic factor (Atri et al., 2002)) is generally recognized. In this regard, we analyzed a database of 542 BC family, encompassing a total of 6762 individuals, including 542 BC afflicted probands.

Accordingly, 29.9% of our studied probands had a positive FH of BC. Also a positive FH of the malignancies other than BC (OM), and all cancers was noted in 53.9% and 64.3% of the families respectively. These crude values demonstrate a considerable overlap between having an FH of BC and having an FH of OM (chi2=102.490, DF=28, p<0.001).

The mean age of the probands was 48.9851±0.9688 years old. The first question to address was whether the positive FH of BC/OM is somehow related to the age of the probands. In other words, considering the age as the most important general single risk factor of cancer, we wanted to determine the relation between the age of the probands and the FH of cancers, since it would be expectable that with increasing the probands' age, the mean relatives' age also increase, which would by itself result in higher cancer incidence.

Using t-test, we found no difference between the mean age of the patients with and without an FH of BC and OM (49.48 versus 48.96 for BC, and 49.70 versus 48.53 for OM). The mean ages of the patients with and without FH of different cancers are presented in Table 8, and as it shows,

Table 4. Frequency of OM According to Sex and Generation. (Numbers in parentheses indicate ratios with probands included in the denominator.)

	Total No. of Cases	Standardized Frequencies (ratios)		
		No. of Cases to Total Male Relatives*	No. of Cases to Total Female Relatives*	No. of Cases to Total Relatives*
1st Generation	61	0.24596	0.22846	0.11844
2nd Generation	239	0.35778	0.32561	0.17047
3rd Generation	131	0.11685 (0.116)	0.09205 (0.067)	0.05149 (0.042)
4th Generation	43	0.05422	0.05149	0.02641
5th Generation	3	0.04411	0.05149	0.02641
All	477	0.16459 (0.164)	0.14358 (0.124)	0.07668 (0.071)

* In the same generation.

Table 5. Distribution of OMs According to Paternal Lines. (Numbers in parentheses indicate numbers of afflicted 1ˢᵗ degree relatives.)

Type of Cancer	Maternal Line	Paternal Line	M/P*	Sister Line	Brother Line	S/B	Total
Gastric	33 (5)	24 (13)	1.37 (2.54)	4 (2)	2 (2)	2 (2/0)	63
Lung	15 (1)	31 (17)	0.48 (1)	1 (1)	2 (2)	0.5 (0/0)	49
Uterus	27 (9)	10	2.7 (1.8)	6 (6)	1	6 (0/1)	44
Leukemia	14 (3)	12 (4)	1.16 (1.37)	3 (2)	7 (0)	0.42 (0.14)	40
Brain	19 (2)	7 (1)	2.71 (2.83)	4 (3)	1 (0)	4 (1)	34
Colorectal	16 (1)	7 (1)	2.28 (2.5)	0 (0)	6 (6)	0/6 (0/0)	30
Esophagus	10 (1)	16 (2)	0.62 (0.64)	0 (0)	2 (2)	0/2 (0/0)	28
Prostate	6	16 (9)	0.37 (0.85)	0	4 (4)	0/4 (0/0)	28
Liver	10 (5)	12 (3)	0.83 (0.55)	1 (1)	2 (2)	0.5 (0/0)	25
Lymphoma	10 (3)	10 (4)	1 (1.16)	0 (0)	3 (3)	0/3 (0/0)	23
Ovary	1 (1)	1	1 (0/1)	2	2	1	7

* Numbers in parenthesis indicates ratios with first degree relatives excluded.

the only significant difference exists between the mean age of the probands with and without an FH of prostate cancer (54.65 versus 48.83). Also, there was no significant correlation between the mean age of the probands, and the mean age of the relatives.

It has been widely accepted that the familial BC cases, tend to manifest in younger age (early-onset BC). Interestingly, this consensus is in contrast with our findings. In our studied BC probands (n=542), 11.99% of cases had their disease diagnosed at or before the age of 36. This percent is considerably higher in comparison with other studies which consider early onset BC as a relatively rare occurring. We noted a positive FH of BC in only 18.5% of these cases which was even much less than the general FH(+) ratio in all the probands regardless of their age. This finding indicates the possibility that early-onset BC cases in our country are less attributable to familial predispositions, and puts forward the environmental factors as the prime cause. A reported high number of different afflicted relatives is observed in rare families (Margaritte-Jeannin et al.,1995). The number of cancer afflicted relatives in our study is shown in Table 9.

Total numbers of the relatives and sex ratios among different generations is presented in Table 1. It is surprising

Table 6. Distribution of Different Cancers According to Generations.

Generation	1st		2nd		3rd		4th		All	
	No.	Freq.	No.	Freq.	No.	Freq.	No.	Freq.	No.	Freq.
Gastric	10	0.0194	41	0.0292	12	0.0038	0	0	63	0.0093
Lung	8	0.0155	29	0.0206	10	0.0032	2	0.0012	49	0.0072
Uterus*	6	0.0224	17	0.0231	20	0.0102	1	0.0011	44	0.0114
Leuk.	2	0.0038	8	0.0057	10	0.0032	15	0.0092	36	0.0053
Brain	2	0.0038	12	0.0085	16	0.0051	4	0.0024	34	0.0050
Color.	5	0.0097	16	0.0114	8	0.0025	1	0.0006	30	0.0044
Eso.	6	0.0116	15	0.0106	6	0.0019	1	0.0006	28	0.0041
Prost.*	5	0.0201	16	0.0239	6	0.0053	1	0.0012	28	0.0096
All	93	0.1805	103	0.0733	75	0.0237	5	0.0029	477	0.0704

* For the uterus and prostate cancers, denominator consists of the total relatives of the same sex.

Table 7. Distribution of Cancers According to the Degree of Family Relationship.

	1ˢᵗ Degree	2ⁿᵈ Degree	3ʳᵈ Degree	4ᵗʰ Degree	Total
Gastric	22 (34.9%)	26 (41.2%)	15 (23.8%)	0 (0%)	63
Lung	20 (40.8%)	17 (34.6%)	11 (22.4%)	1 (2%)	49
Uterus	13 (29.5%)	16 (36.3%)	13 (29.5%)	2 (4.5%)	44
Brain	12 (35.2%)	12 (35.2%)	9 (26.4%)	1 (2.9%)	34
Colorectal	8 (26.6%)	9 (30%)	12 (40%)	1 (3.3%)	30
Esophagus	5 (17.8%)	15 (53.3%)	8 (28.5%)	0 (0%)	28
Prostate	13 (46.4%)	8 (28.5%)	7 (25%)	0 (0%)	28

Table 8. Mean Age of FH(+) and FH(-) Probands According to Type of Cancers.

		Gastric	Lung	Uterus	Leuk.	Brain	Color.	Eso.	Prost.	Liver	Lymph.	Ovary
	FH(+)	48.36	49.41	51.81	52.13	47.71	50.29	51.77	54.65	49.04	52.91	53.57
	FH(-)	49.20	49.09	48.91	48.88	49.21	49.05	48.97	48.83	49.12	48.94	49.06
Mean of Diff.		-.846	0.322	2.905	3.246	-1.498	1.237	2.800	5.823	-.082	3.965	4.508
95% CI of Diff.	Lower	-4.154	-3.047	-.834	-.491	-5.555	-3.158	-1.589	1.376	-4.927	-.765	-3.945
	Upper	2.462	3.693	6.645	6.984	2.558	5.632	7.190	10.270	4.763	8.697	12.962

that the male/female (M/F) ratio in 3rd generation is dramatically less than other generations (0.5752). This might be partly explained because of the nature of our pedigrees (based upon BC-probands who are mostly females), but by exclusion of probands, still the same pattern persists (M/F ratio = 0.7877).

Considering the number of BCs in pedigrees, 2nd generation followed by 3rd generations showed highest crude frequencies (542 BC probands excluded), and 3rd followed by 2nd generations (the BC probands included). However, the standardized ratios revealed the leading generations of BC involvement to be 2nd and 1st (probands excluded); and 3rd and 2nd generations (probands included).

Therefore, by including the probands (Table 2), the highest incidence is reflected in 3rd generation, and so a cascade manifestation through the 1st to 3rd generations could be noted.

When we considered the total number of relatives through 1st to 4th generations, the same pattern was revealed, but disparity between 1st & 2nd generations decreased (Table 2).

The most frequent BC involvement among 1st; 2nd; 3rd; and 4th degree relatives was noted in 3rd; 2nd; 3rd and 3rd generations respectively (Table 3). As far as the frequency of BC concerns, this manifestation reveals to be focused on 2nd-degree/ 2nd-generation (i.e. mostly aunts), and 3rd-degree/ 3rd-generation relatives (i.e. 1st cousins), however, again this finding is explainable to some extend, by the fact that the total number of relatives in the above-cited strata is expected to be higher.

Table 9. The Number of Cancer Afflicted Relatives in Total Studied Pedigrees.

Number of Cancers	Frequency	Percent	Valid Percent	Cumulative Percent
.0	185	34.1	35.7	35.7
1.0	154	28.4	29.7	65.4
2.0	93	17.2	18.0	83.4
3.0	40	7.4	7.7	91.1
4.0	23	4.2	4.4	95.6
5.0	14	2.6	2.7	98.3
6.0	3	.6	.6	98.8
7.0	3	.6	.6	99.4
8.0	1	.2	.2	99.6
10.0	2	.4	.4	100.0
Total	518	95.6	100.0	

It is notable that in order to achieve the similar finding in 3rd generation, we had to move one step further (2nd degree to 3rd degree). But when we have a close look at 1st degree relatives, we find almost similar frequencies in 2nd and 3rd generations.

Considering the 1st generation relatives, grand parents are relatively less involved, and that is the 3rd degree relatives in 1st generation (mostly parents' aunts) who show the most involvement, similar to the distribution of afflicted 3rd generation relatives (mostly probands' aunts).

In addition, the least involvement in the probands' generation (i.e. 3rd generation) was observed in 2nd degree and 4th degree relatives. Meanwhile, involvement of 2nd degree relatives was two-fold more than 4th degree relatives in this generation (6/3) (Table 3).

Relatively low frequency of stepsibling due to second marriages (2nd degree) in 3rd generation could be held responsible for this alternative involvement pattern.

Regarding OMs, it was noted that 2nd generation relatives (followed by 1st generation relatives) harbored the greatest ratio of cancer involvement. In contrast, the 3rd generation (which is representative of the most frequent BC involvement) demonstrated less frequent involvement of different types of OMs (table 4).

Standardized ratio of OM involvement in 2nd to 3rd generation (0.17047/ 0.05149) is 3.31 (4.01, probands included in the denominator) (Table 4). The same ratio for BC (0.06419/0.03183) was 2.01 (0.69. probands included). Considering parental lines, highest maternal to paternal (M/P) ratios was observed for brain (2.7), uterus (2.8), followed by colorectal (2.28) cancers. Excluding first degree relatives (to minimize the possible effects of unequal sex ratio for different cancers), highest M/P ratios was noted for Brain (2.83), gastric (2.54), and colorectal (2.5) cancers. Therefore, occurrence of brain tumors as the cancer with the highest M/P ratio was predominant regardless of exclusion or inclusion of the first degree relatives (Table 5).

When we considered the lowest M/P ratio (i.e. highest P/M ratio), we noted that the prostate cancer (0.37), followed by lung cancer (0.48) pose the minimum ratio. However and excluding first degree relatives, the least M/P ratio was noted for liver cancer (0.55). This finding demonstrates that the majority of prostate cancer cases in our families were occurred among 1st degree relatives (i.e. BC patients' fathers) (Table 5).

As far as distribution of OM's across various generations concerns, the most frequent cancers in 1st, 2nd, 3rd, and 4th generations were gastric, gastric, uterus, and hematopoeitic

system cancers respectively (Table 6). According to type of cancers, the highest numbers (and highest frequency) of gastric, lung, uterus, hematopoeitic system, brain, colorectal, esophagus, prostate, and all cancers were noted in 2nd(1st), 2nd(2nd), 3rd(2nd), 4th(4th), 3rd(2nd), 2nd(2nd), 2nd(1st), 2nd(2nd), and 2nd(2nd) generations (Table 6).

Regarding OM distribution according to the degree of relativity, highest number of gastric, lung, uterus, brain, colorectal, esophagus, and prostate cancers was noted in 2nd, 1st, 2nd, equally 1st and 2nd, 3rd, 2nd, and 1st degree relatives respectively (Table 7).

Conclusions

Family history (FH) of malignancies is one of the most important, yet controversial risk factors of cancers, including breast cancer (BC). In present study we tried to investigate malignancies involvement pattern in relatives of 542 BC patients.

Although the frequency of consanguineous marriages is relatively high in Iran (14% in probands' parents in present study), there was no relation between consanguinity and cancer incidence (data not presented here, see also Atri., et al, 2002).

In our study, early-onset BC incidence was higher than other studies performed in other populations (11.99%). Unlike the previous reports linking early onset BC occurrence and positive FH of BC, we found a less positive FH ratio in our early-onset BC cases. To our surprise, we had the highest numbers of isolated (non-familial) BC cases, in patients who were younger than 36, or older than 70 years old. The later can be explainable by the accommodation of somatic genetic hits through the longer years, but the former finding (together with the above-mentioned higher early-onset BC occurrence in our population) raises the possibility of environmental factor(s) affecting young females in Iran and which predispose(s) them to an early-onset BC.

Age is considered as a general risk factor of malignancies. In this study, we were facing the risk of a possible relation between probands' older age and more cancer occurrence in relatives (due to relatives older age), which could confound the analysis. Therefore, we compared the mean age of the probands with and without family history of cancers, and found that except for FH of prostate cancer, there was no significant difference between mean age of FH(+) and FH(-) probands. Also, mean age of the relatives was independent of the mean age of the probands.

The highest frequency of BC was noted in 3rd generation, followed by 2nd and 1st generations (with a decrement of ~1.5 fold). Thus, it would be expectable to witness an even higher frequency in 4th generation, but the general younger age of the relatives in this generation might have prevented this to happen. This finding contradicts another expectation, since BC incidence increases with age, and it would be reasonable to have more BC cases in older generations. Our analysis of the pedigrees revealed that the most BC-involved relatives consist of aunts, first cousins, sisters, and

mothers respectively. However, considering the total number of relatives in each of these categories, the order will change, so that probands' mothers and sisters become the most involved relatives (data not presented here). Also, BC involvement in maternal-line was associated with more breast cancers in patients.

The most frequent OMs in our BC pedigrees were gastric, lung, uterus, hematopoeitic system, brain and colorectal cancers, which are rather in concordance with cancers in general population, though considering BC, the later will become the most frequent malignancy among BC pedigrees. Also, excess of lung and uterus cancers in BC probands as cited in other reports (Schildkraut et al., 1989; Peto et al., 1996) was not confined to younger age groups in present study.

When we compared the present population with the Parses community (Persian Zoroastrians who fled to India in 7th century AD), it was noted that incidence of lymphoma in our population was much lower (data presented in 3rd global cancer organizations conference, Brighton, UK, 2001). This finding, together with common genetic grounds suggests some possible environmental factors leading to an increased lymphoma incidence in that population.

Unlike BC, the highest frequency of OMs was noted in 2nd followed by 1st generations. Also, ratio of OM cases in 2nd to 3rd generations was much higher than the ratio of BC cases in 2nd to 3rd generations.

Brain, gastric, and colorectal cancers (respectively) tended to afflict maternal-line relatives much more than paternal-line relatives. On the other hand, liver cancer was the malignancy with most tendencies to afflict the paternal-line relatives (1st degree relatives excluded). Also, majority of prostate cancer cases were probands' fathers.

Although gastric cancer was by far the most frequent OM across pedigrees, uterus cancer, and hematopoeitic system (leukemia) dominated over gastric cancer through 3rd and 4th generations respectively. Considering the rather limited available information in 4th generation due to the young age of relatives in this generation, dominancy of leukemia is intriguing and therefore, BC involvement in mothers might be put forward as a predictive factor for developing leukemia in 4th generation. This hypothesis is being tested in a case-control study.

Colorectal cancer is sometimes regarded as an accompanying malignancy in BC pedigrees. Here, we found out that the highest number of colorectal cancers were among 3rd degree relatives, mostly in maternal-line relatives, and also in 2nd generation.

In line with the fact that gastric cancer was by far the most frequent OM at all, it also dominated among 1st, 2nd, and 3rd degree relatives. So far, most of the studies couldn't establish an evidence-based genetic frame for gastric cancer, and this has redirected much attention towards environmental factors. Our finding of a high frequency of gastric cancer in our population might be attributable to high frequency of this cancer in Iran, which requires more investigations. Just as a descriptive note, it might be notable that the occurrence

of lung, uterus, prostate and brain cancers in 1st degree relatives was higher.This descriptive study reports on the involvement pattern of malignancies in relatives of BC-afflicted patients. Detailed analytic studies of these data is being carried out and will be published subsequently.

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