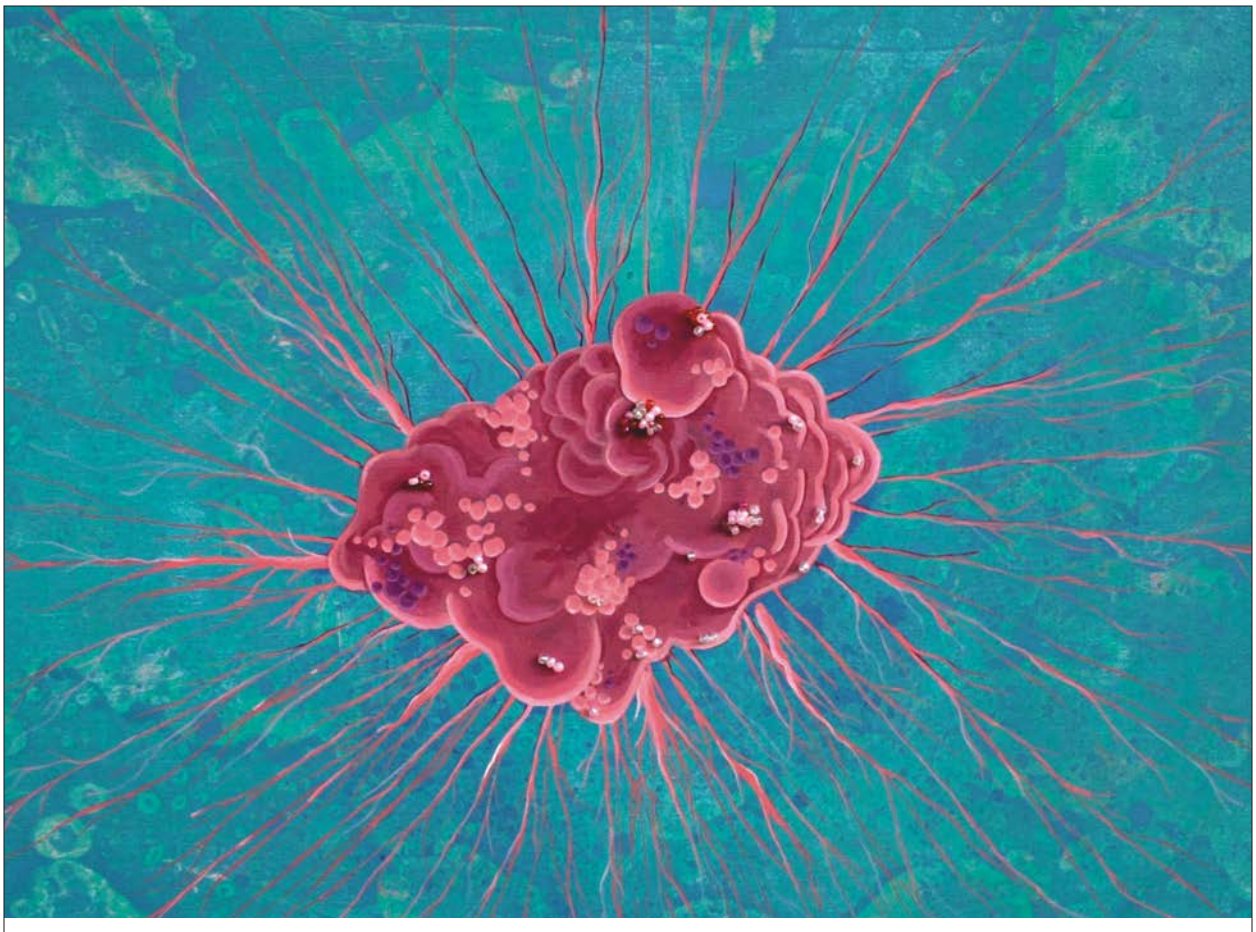

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Risk Factors for Breast Cancer in Iranian Women: A Case-Control Study

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Abstract: The objective of the present study was to investigate risk factors for breast cancer in Iranian women. A case-control study was conducted from April 2004 to May 2007 in Tehran, Iran. Demographical data and risk factor related information were collected using a short structured questionnaire. In all, 150 women with breast cancer and 147 control women were interviewed. In multivariate analysis, only body mass index or BMI age at menarche, age at marriage, race, ABO and Rh blood groups and family history of breast cancer were associated with significantly increased risk for breast cancer ($p<0.05$). The findings of the present study suggest that family history and marital status may have an impact on the incidence of breast cancer in Iranian women.

Key words: Breast cancer, BMI, risk factors

INTRODUCTION

Breast cancer is the most common cancer among women worldwide. Incidence rates increased rapidly predominantly in women 50 and older (American Cancer Society, 2005) in the 1980s due to the increased detection of smaller, earlier-stage cancers with the widespread adoption of the screening of mammography among asymptomatic women (American Cancer Society, 2001). A portion of this increase can be attributed to changes in reproductive patterns, such as delayed childbearing and having fewer children (increased life expectancy). Though, at one of the lowest incidence rates in Iran as in other Asian countries, during last four decades, increasing its incidence rate has made breast cancer one of the most frequent malignancies among Iranian women (Behjati *et al*., 2005). Breast cancer affects Iranian women at least one decade younger than their counterparts in developed countries (Harirchi *et al*., 2004; Lin *et al*., 2008). The mortality rate of breast cancer was 5.8 per 100,000 women in Tehran in 1998 (Mousavi *et al*., 2007), 2.5 per 100,000 for female population and 7762 years life lost in the 18 provinces of Iran in 2001 (Najafi *et al*., 2005). Developing countries hope to be on the threshold of eliminating breast cancer as a major public health threat (Cady, 2000). Early detection of breast cancer remains an important challenge to health professionals. Genetic factors such as ER genes polymorphisms also considered before as an effective risk factor with positive effects (Vasconcelos *et al*., 2002; Heldring *et al*., 2007; Wang *et al*., 2007; Holst *et al*., 2007) and negative effects (Slattery *et al*., 2007; Gonzalez *et al*., 2008; Einarsdóttir Darabi *et al*., 2008) in the different studies.

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Geographical variations in incidence and mortality rates of breast cancer suggest that the known risk factors for breast cancer may vary in different parts of the world and that environmental factors are of greater importance than genetic factors (McPherson *et al*., 2000). For instance, in Iran it has been shown that, even after adjusting for age, young women are at relatively higher risk for developing breast cancer than are their Western counterparts (Harirchi *et al*., 2000). Thus, study of risk factors for breast cancer in Iranian women is important and might contribute to current knowledge on this important topic. This may be one of the first studies on the role of hereditary factors in the development of the breast cancer in Iranian patients. The aim of the present study was to examine the relationship between common risk factors and development of breast cancer in Iranian women population to improve the breast cancer care.

MATERIALS AND METHODS

A case-control study was conducted from April 2004 to May 2007 in Tehran, Iran. The Ethic Committee Agreement was obtained from Tehran University of Medical Sciences. The 150 new cases were casual, newly diagnosed breast cancer patients mostly living in Tehran and they were entered into the study if they had a confirmed pathological breast cancer. All patients were admitted to the Imam Khomeini Hospital Complex (a large teaching and general hospital in the central district of Tehran) and were examined by gynecologist in a program of primarily Clinical Breast Exam (CBE) and further an mammography were taken by radiologist (Fig. 1) and those who were diagnosed with cancer were referred to our several clinics of the Cancer Institute. The 147 control women were recruited from female patients without any history of breast problems or neoplastic disease and not had any other cancers. Women with hysterectomy and artificial menopause or exposed to any kind of radiation and chemotherapy in their life time were excluded from the study. By the permission from hospital ethics committee, all patients provided written Informed Consent to participate in that protocol before entering into the present study.

Demographical and risk factor data were collected using a short structured questionnaire, including information on: place of birth, weight, height, profession, religion, age at menarche, marital status (single, married), age at marriage, age at the first child delivery, number of deliveries, number of children, average period of breast feeding (month), age at menopause (in the case of reaching menopause), onset age of breast cancer (before 40 years old, between 40-50 years after menopause), parent's marital status (first degree relative, second degree relative, third degree relative, not relative),

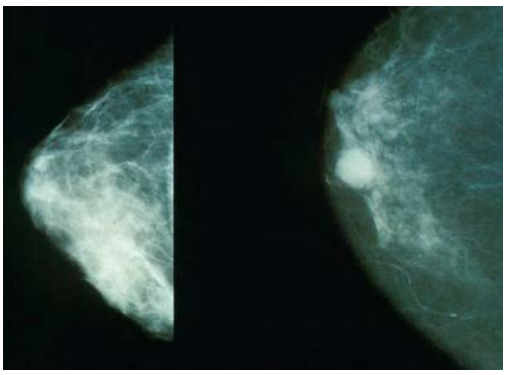

Fig. 1: Mammograms: Left, normal; right, a small mass

race (Fars, Turkish, Kurdish, Lor, Arab, Gilaki, Mazani), ABO and rhesus blood groups (A^+, B^+, AB^+, O^+, A^-, B^-, AB^-, O^-), family history of breast cancer (mother, sister(s), daughter(s), non), previous record for the other cancer(s), Lymph Node (LN) Metastases, type of breast cancer (unilateral, bilateral), stage of breast cancer at the time of testing and Estrogen Receptor (ER) expression in breast cancer tissue.

Women were classified as menopausal if they had not menstruated during the 6 months before the date of data collection. This information was obtained by interviewing with patients and family members. The distributions of selected demographic characteristics and major risk factors for breast cancer of whole subjects and cases are shown in Table 1.

Table 1: The distributions of selected demographic characteristics and major risk factors for breast cancer of whole study population: breast cancer versus control groups

Characteristics	Case No. (%)	Control No. (%)
Age (years)		
</=40	52(41.3)	98(57.3)
>40	74(58.7)	73(42.7)
BMI (kg m^{-2})		
</=18.5 (Underweight)	5(3.3)	9(6.1)
18.6-24.9 (Normal)	57(38.0)	90(61.2)
25.0-29.9 (Overweight)	55(36.7)	35(23.8)
>30.0 (Obese)	33(22.0)	13(8.9)
Profession		
Housewife	129(86.0)	27(18.3)
Student	2(1.3)	32(21.8)
Others	19(12.7)	88(59.9)
Religion		
Moslem	148(98.7)	146(99.3)
Non-Moslem	2(1.3)	1(0.7)
Age at menarche (years)		
</=12	60(40.0)	36(24.5)
>12	90(60.0)	111(75.5)
Marital status		
Married	140(93.3)	99(67.3)
Single	10(6.7)	48(32.7)
Age at marriage (years)		
</=20	92(65.7)	40(40.4)
>20	48(34.3)	59(59.6)
Age at first child delivery (years)		
</=30	124(92.5)	89(92.7)
>30	10(7.5)	7(7.3)
No. of deliveries in married individuals		
0	6(4.3)	5(5.1)
1	9(6.4)	37(37.4)
2	21(15.0)	29(29.2)
>/=3	104(74.3)	28(28.3)
Child status in married individuals		
Yes	134(95.7)	94(94.9)
No	6(4.3)	5(5.1)
Average lactation term in married individuals with child delivery		
Not breastfed	3(2.2)	2(2.1)
</= one year	36(26.9)	38(40.4)
>1 year	95(70.9)	54(57.5)
No. of children in married individuals		
0	6(4.3)	5(5.1)
1	10(7.1)	38(38.4)
2	30(21.4)	31(31.3)
>/=3	94(67.2)	25(25.2)

Table 1: Continued

Characteristics	Case No. (%)	Control No. (%)
Menopause status		
Yes	59(39.3)	18(12.2)
No	91(60.7)	129(87.8)
Age at menopause (years)		
</=50	47(79.7)	11(61.1)
>50	12(20.3)	7(38.9)
Onset age of breast cancer (years)		
<40	48(32.0)	-
>/=40	66(44.0)	-
After menopause	36(24.0)	-
Parent's marriage status		
First-degree relative	24(16.1)	13(8.8)
Second-degree relative	-	7(4.8)
Far-relative	13(8.7)	11(7.5)
Non-relative	112(75.2)	116(78.9)
Race		
Arabs and Armani	3(2.0)	-
Fars	60(40.0)	88(59.9)
Lor and Kurdish	18(12.0)	9(6.1)
Turkish	46(30.7)	39(26.5)
Gilaki and Mazani	23(15.3)	11(7.5)
ABO and Rh blood groups		
A^+	27(18.0)	39(26.5)
B^+	12(8.0)	31(21.1)
AB^+	6(4.0)	15(10.2)
O^+	100(66.7)	47(32.0)
A^-	-	4(2.7)
B^-	2(1.3)	4(2.7)
AB^-	-	1(0.7)
O^-	3(2.0)	6(4.1)
ABO blood groups		
A	27(18.0)	43(29.2)
B	14(9.3)	35(23.8)
AB	6(4.0)	16(10.9)
O	103(68.7)	53(36.1)
Rh and blood groups		
Positive	145(96.7)	132(89.8)
Negative	5(3.3)	15(10.2)
Family history of breast cancer		
First-degree family affected	19(12.7)	-
Not affected	131(87.3)	147(100.0)
First-degree family history of breast cancer		
Mother	8(42.1)	-
Sister	6(31.6)	-
Daughter	4(21.0)	-
Mother and sister	1(5.3)	-
Other cancer affected status		
Yes	3(2.0)	-
No	147(98.0)	147(100.0)
Lymph node metastases		
Yes	23(15.3)	-
No	127(84.7)	-
Type of breast cancer		
Unilateral	142(94.7)	-
Bilateral	8(5.3)	-
Stage of breast cancer of at the time of testing		
Stage II	133(88.7)	-
Stage III	15(10.0)	-
Stage IV	2(1.3)	-
ER expression in breast cancer tissue		
Positive	40(26.7)	-
Negative	92(61.3)	-
Not studied	18(12.0)	-

χ^2 testing was employed to assess the influence of risk factors status on features of breast cancer (Breslow and Day, 1980; Rothman, 1998). Statistical analysis was performed using SPSS software (version 11.5) for Windows; SPSS Inc., Cary, NC, USA). $p<0.05$ was considered statistically significant. Those risk factors that were significantly associated with breast cancer were entered into a forward selection multivariate logistic regression analysis.

RESULTS

The patients were mostly above 44 years (44%) and only 15.3% had lymph node metastases as it was expected from the stage of cancer that 88.7% were in stage II at the time of testing (Table 2).

The breast cancer cases (n = 150) with median age 47.49±11.43 years and control group (n = 147) with median age 40.75±10.54 years. Median BMI among case group is higher (26.28±5.09, overweight) than control group (23.09±1.46, normal) and also the median start age of menarche is lower in case (12.94±1.62 years) than control (13.4.07±1.46 years) groups. Age at marriage another risk factor in developing breast cancer is also lower in case (median age 19.24±4.72 years) than control (median age 22.14±4.56 years) groups (Table 3).

Among these factors; BMI (</=18.5 or underweight, 18.6-24.9 or normal, 25-29.9 or overweight and >30 or obese), profession (housewife, student and others), age at menarche (</=12 and >12 years), age at marriage (</=20 and >20 years), number of deliveries in married individuals (0, 1, 2, >/=3), average lactation term in married individuals with child delivery (not breastfed, </=1 year and >1 year), number of children in married individuals (0, 1, 2, >/=3), race (Arab and Armani, Fars, Lor and Kurdish, Turkish and Gilaki and Mazani), ABO and Rh blood groups and family history of breast cancer (first-degree family include:mother, sisters, daughters and not affected) the difference between case and control groups was statistically significant ($p<0.05$) (Table 4).

Table 2: Clinical characteristics of the 150 breast cancer patients in the study

	Case	
Characteristics	Frequency	Percent
Onset age of breast cancer (years)		
<40	48	32.0
>/=40	66	44.0
After menopause	36	24.0
Total	150	100.0
Lymph node metastasis		
Yes	23	15.3
No	127	84.7
Total	150	100.0
Type of breast cancer		
Unilateral	142	94.7
Bilateral	8	5.3
Total	150	100.0
Stage of breast cancer at the time of testing		
Stage II	133	88.7
Stage III	15	10.0
Stage IV	2	1.3
Total	150	100.0
ER expression in breast cancer tissue		
Positive	40	26.7
Negative	92	61.3
Not studied	18	12.0
Total	150	100.0

Table 3: The distributions of selected demographic characteristics and major risk factors for breast cancer of whole study population: breast cancer versus control groups

	Groups		
Characteristic	Case (n = 150)	Control (n = 147)	Total (n = 297)
Age (years)	47.49±11.43	40.75±10.54	44.15±11.49
Weight	68.41±13.21	61.36±10.63	64.92±12.49
Height (cm)	161.46±6.01	160.61±5.21	161.04±5.64
BMI (kg m^{-2})	26.28±5.09	23.80±4.07	25.05±4.80
Age at menarche (years)	12.94±1.62	13.24±1.25	13.09±1.46
	Groups		
Characteristic[a]	Case (n = 140)	Control (n = 99)	Total (n = 239)
Age at marriage (years)	19.24±4.72	22.14±4.56	20.44±4.88
No. of deliveries	3.92±2.10	2.03±1.40	3.14±2.09
No. of children	3.44±1.74	1.95±1.26	2.82±1.72
	Groups		
Characteristic[b]	Case (n = 134)	Control (n = 96)	Total (n = 230)
Age at first child delivery (years)	21.63±5.46	24.35±4.59	22.77±5.28
Average lactation term (years)	17.91±8.27	16.01±13.13	17.12±10.59

(a): The distributions of selected demographic characteristics and major risk factors for breast cancer of married individuals: breast cancer versus control groups, (b): The distributions of selected demographic characteristics and major risk factors for breast cancer of married individuals with children: breast cancer versus control groups

Table 4: Frequencies distribution of selected demographic characteristics and major risk factors in the study population: breast cancer versus control groups

	Groups						
	Case		Control		Total		
Characteristic	Frequency	Percent	Frequency	Percent	Frequency	Percent	Test result
Age (years)							
</=40	52	41.3	98	57.3	150	50.5	$\chi^2 = 7.417$
>40	74	58.7	73	42.7	147	49.5	p = 0.006
Total	126	100.0	171	100.0	297	100.0	
BMI (kg m^{-2})							
</=18.5 (Underweight)	5	3.3	9	6.1	14	4.7	$\chi^2 = 21.663$
18.6-24.9 (Normal)	57	38.0	90	61.2	147	49.5	p = 0.001
25-29.9 (Overweight)	55	36.7	35	23.8	90	30.3	
>30 (Obese)	33	22.0	13	8.9	46	15.5	
Total	150	100.0	147	100.0	297	100.0	
Profession							
Housewife	129	86.0	27	18.3	156	52.5	$\chi^2 = 137.642$
Student	2	1.3	32	21.8	34	11.5	p = 0.001
Others	19	12.7	88	59.9	107	36.0	
Total	150	100.0	147	100.0	297	100.0	
Religion							
Moslem	148	98.7	146	99.3	294	99.0	$\chi^2 = 0.136$
Non-Moslem	2	1.3	1	0.7	3	1.0	p = 0.574
Total	150	100.0	147	100.0	297	100.0	
Age at menarche (years)							
</=12	60	40.0	36	24.5	96	32.3	$\chi^2 = 8.165$
>12	90	60.0	111	75.5	201	67.7	p = 0.004
Total	150	100.0	147	100.0	297	100.0	
Marital status							
Married	140	93.3	99	67.3	239	80.5	$\chi^2 = 11.992$
Single	10	6.7	48	32.7	58	19.5	p = 0.001
Total	150	100.0	147	100.0	297	100.0	
Age at marriage (years)							
</=20	92	65.7	40	40.4	132	55.2	$\chi^2 = 14.962$
<20	48	34.3	59	59.6	107	44.8	p = 0.001
Total	140	100.0	99	100.0	239	100.0	

Table 4: Continued

	Groups						
	Case		Control		Total		
Characteristic	Frequency	Percent	Frequency	Percent	Frequency	Percent	Test result
Age at first child delivery (years)							
</=30	124	92.5	89	92.7	213	92.6	$\chi^2 = 0.002$
>30	10	7.5	7	7.3	17	7.4	p = 0.961
Total	134	100.0	96	100.0	230	100.0	
No. of deliveries (married individuals)							
0	6	4.3	5	5.1	11	4.6	$\chi^2 = 41.493$
1	9	6.4	37	37.4	46	19.3	p = 0.001
2	21	15.0	29	29.2	50	20.9	
>/=3	104	74.3	28	28.3	132	55.2	
Total	140	100.0	99	100.0	239	100.0	
Child status (married individuals)							
Yes	134	95.7	94	94.9	228	95.4	$\chi^2 = 26.831$
No	6	4.3	5	5.1	11	4.6	p = 0.781
Total	140	100.0	99	100.0	239	100.0	
Average lactation term (married individuals with child delivery)							
Not breastfed	3	2.2	2	2.1	5	2.2	$\chi^2 = 3.538$
</= 1 year	36	26.9	38	404.0	74	32.4	p = 0.060
>1 year	95	70.9	54	57.5	149	65.4	
Total	134	100.0	94	100.0	228	100.0	
No. of children (married individuals)							
0	6	4.3	5	5.1	11	4.6	$\chi^2 = 38.285$
1	10	7.1	38	38.4	48	20.1	p = 0.001
2	30	21.4	31	31.3	61	25.5	
>/=3	94	67.2	25	25.2	119	49.8	
Total	140	100.0	99	100.0	239	100.0	
Menopause status							
Yes	59	39.3	18	12.2	77	25.9	$\chi^2 = 28.367$
No	91	60.7	129	87.8	220	74.1	p = 0.001
Total	150	100.0	147	100.0	297	100.0	
Age at menopause (years)							
</=50	47	79.7	11	61.1	58	75.3	$\chi^2 = 2.520$
>50	12	20.3	7	38.9	19	24.7	p = 0.112
Total	59	100.0	18	100.0	77	100.0	
Parent's marriage status							
First-degree relative	24	16.1	13	8.8	37	12.5	$\chi^2 = 1.285$
Second-degree relative	-	-	7	4.8	7	2.4	p = 0.257
Far-relative	13	8.7	11	7.5	24	8.1	
Non-relative	112	75.2	116	78.9	228	77.0	
Total	149	100.0	147	100.0	296	100.0	
Race							
Arab and Armani	3	2.0	-	-	3	1.0	$\chi^2 = 7.351$
Fars	60	40.0	88	59.9	148	49.8	p = 0.007
Lor and Kurdish	18	12.0	9	6.1	27	9.1	
Turkish	46	30.7	39	26.5	85	28.6	
Gilaki and Mazani	23	15.3	11	7.5	34	11.4	
Total	150	100.0	147	100.0	297	100.0	
ABO and Rh blood groups							
A^+	27	18.0	39	26.5	66	22.2	$\chi^2 = 25.144$
B^+	12	8.0	31	21.1	43	14.5	p = 0.023
AB^+	6	4.0	15	10.2	21	7.1	
O^+	100	66.7	47	32.0	147	49.5	
A^-	-	-	4	2.7	4	1.4	
B^-	2	1.3	4	2.7	6	2.0	
AB^-	-	-	1	0.7	1	0.3	
O^-	3	2.0	6	4.1	9	3.0	
Total	150	100.0	147	100.0	297	100.0	

Table 4: Continued

	Groups						
	Case		Control		Total		
Characteristic	Frequency	Percent	Frequency	Percent	Frequency	Percent	Test result
ABO blood groups							
A	27	18.0	43	29.2	70	23.6	$\chi^2 = 33.201$
AB	6	4.0	16	10.9	22	7.4	$p = 0.001$
B	14	9.3	35	23.8	49	16.5	
O	103	68.7	53	36.1	156	52.5	
Total	150	100.0	147	100.0	297	100.0	
Rh blood groups							
Positive	145	96.7	132	89.8	277	93.3	$\chi^2 = 5.813$
Negative	5	3.3	15	10.2	20	6.7	$p = 0.016$
Total	150	100.0	147	100.0	297	100.0	
Family history of breast cancer							
First-degree family affected	19	12.7	-	-	19	6.4	$\chi^2 = 19.893$
Not affected	131	87.3	147	100.0	278	93.6	$p = 0.001$
Total	150	100.0	147	100.0	297	100.0	
Family history of breast cancer							
Mother	8	5.3	-	-	8	2.7	$\chi^2 = 27.231$
Sister	6	4.0	-	-	6	2.0	$p = 0.001$
Daughter	4	2.7	-	-	4	1.3	
Mother and sister	1	0.7	-	-	1	0.3	
Not affected	131	87.3	147	100.0	278	93.7	
Total	150	100.0	147	100.0	297	100.0	
Other cancer affected status							
Yes	3	2.0	-	-	3	1.0	$\chi^2 = 2.960$
No	147	98.0	147	100.0	294	99.0	$p = 0.085$
Total	150	100.0	147	100.0	297	100.0	

DISCUSSION

In this study among 150 cancer patients participants 41.3% were below 40 years old and among 147 control group 57.3% were below 40 years old. When the obesity was considered as a risk factor in developing breast cancer (Barlow *et al*., 2006), it revealed that among cancer patients the obesity was statistically significant ($\chi^2 = 21.663$, $p = 0.001$) twofold higher (22.0%) than healthy individuals (8.9%). Age at menarche below 12 years old as another risk factor for breast cancer (Chen *et al*., 2006), it was shows significantly ($\chi^2 = 8.165$ $p = 0.004$) much higher among breast cancer individuals (40.0%) than control group (24.5%). Also age at marriage below 20 years old as increasing risk in developing breast cancer (Chen *et al*., 2006), revealed significantly ($\chi^2 = 14.692$, $p = 0.001$) higher again among breast cancer individuals than control group (65.7 and 40.4%, respectively).

Among all different races, it was found among two groups of races; Lor and Kurdish in Western part of Iran (12.0% versus 6.1%) and Gilaki and Mazani in Northern part of Iran (15.3% versus 7.5%) breast cancer individuals were significantly ($\chi^2 = 7.351$, $p = 0.007$) two fold higher than normal individuals. In eight different ABO and Rh blood groups, among individuals with O^+ blood group, breast cancer patients were twofold higher than healthy individuals (66.7 and 32.0%, respectively) ($\chi^2 = 25.144$, $p = 0.023$).

Earlier studies were shown that positive family history of breast cancer is risk factors for breast cancer in Iran (Ebrahimi *et al*., 2002). This is in accordance with other research findings indicating that a positive family history of breast cancer is a strong risk factor for breast cancer at young age (Montazeri *et al*., 2003; Pharoah *et al*., 1997), although this has a comparatively small effect on the absolute lifetime incidence of and mortality from breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001). In this study, family history as a strong factor in developing breast cancer in the life time, was statistically significant differences ($\chi^2 = 27.231$, $p = 0.001$) between cancer

patients and the control individuals, with 5.3% when mother affected, 4.0% when sister affected and 2.7% when daughter affected. However, with regard to the findings from the present study, one may argue that the relatively high proportion of young breast cancer cases in Iran is most likely due a to a young population structure and to a combination of high age at menarche and low age at first pregnancy, which are protective in later life. Evidence from the USA (Lin *et al*., 2002) also suggests that, in some Asian subgroups such as the Vietnamese, women diagnosed with breast cancer tend to be younger than those from other racial or ethnic groups, with half of the diagnoses occurring in women younger than 50 years; this needs further exploration.

These findings presented here, are shown that unmarried women were at higher risk for breast cancer and is similar to other studies (Chen *et al*., 2006). In most studies single and nulliparous married women were found to have a similar increased risk for breast cancer as compared with parous women of the same age (Rosner *et al*., 1994). Thus, one may argue that marital status by itself is not a determining factor for increased or reduced breast cancer risk and rather the main protective effect is from early first full-term pregnancy. However, in the present study no association with parity emerged when multivariate analysis was performed same as earlier studies (Chen *et al*., 2006). Evidence suggests that there is an interaction between marital status and parity (McCredie *et al*., 1998), supporting a dual effect of parity on breast cancer risk with pregnancy.

Studies have shown that interactions between age, family history of breast cancer and parity might exist (Andrieu *et al*., 2000). In addition, studies have reported that nulliparity reduces risk for breast cancer at younger age and elevates risk in the elderly (Lipworth, 1995; Tavani *et al*., 1999).

Finally, one should be aware of the limitations of the present study, including case and control ascertainment and representation. Although the results cannot be generalized, the findings suggest that the associations between some known risk factors for breast cancer may differ in Iran as compared with Western countries and that familial breast cancer in young Iranian breast cancer patients deserves further investigation.

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