RESEARCH ARTICLE

The Investigation of Risk Factors Impacting Breast Cancer in Guilan Province

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Abstract

Introduction: Breast cancer is multifactorial therefore more recognition of risk factors is important in its prevention. **Objective:** This study was conducted in order to determine the factors influencing breast cancer in women referred to health centers in Guilan province in 2015-2016. **Method:** In a case- control study, 225 women with breast cancer were investigated. The control group consisted of 225 healthy women of the relatives (third-rank) whose phone numbers were obtained from the patients. Data were collected through telephone interviews. **Results:** The risk of breast cancer raised in women who have a family history of other cancers (OR= 3.5; 95% CI= 1.96-6.6) ,exposure to X-Ray (OR= 2.5; 95% CI=1.1-5.5), having more than 4 children (OR= 2.695% CI=1.2-4.8), age more than 36 years at first pregnancy(OR=2.3; 95% CI=0.7-5.1),primary levelof education (OR= 5.4;95% CI=2.8-11.2) and inadequate intake of fruit (OR=1.5; 95% CI=1-2.2). Also, presence of the following factors reduced breast cancer risk: regular menstruation (OR= 0.66; CI=0.4-0.9), duration of breastfeeding more than 12 months, less than 6 months and 7-12 months (OR=0.23; 95% CI=0.09-0.59 , OR=0.29; 95% CI=0.17-0.49 and OR=0.03; 95% CI=0.01-0.08) and parity (OR=0.4; 95% CI=0.27-0.83) In multiple linear regression analysis of higher education (OR=0.16; 95% CI=0.03-0.77), using contraceptives for more than 16 years (OR=2.3; 95% CI=1.4-3.9), family history of other cancers (OR=6.1; 95% CI=1.9-19.3) and a history of X-Ray exposure (OR=4.4; 95% CI=1.07-18.1) were considered as predictive factors. **Conclusion:** The results of this study emphasize the importance of informing women about breast cancer risk factors. So, identification of these risk factors is required as important means of prevention and treatment of breast cancer.

Keywords: Prevention- risk factors- breast cancer- case-control studies- Iran

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Introduction

Breast cancer is the most rampant cancer among women (Yaghmaeiet al., 2008, Baneshiet al., 2012, Haghighat et al., 2012).This cancer is the most common cancer in both developed and developing countries (Nafissi et al., 2012).Furthermore, aboutfive thousand people are diagnosed with breast cancer in Iran annually (Vostakolaei et al., 2013).and21.4 percent of the total reported cancers is breast cancer (Tahrgorabyet al., 2014).In recent decade, the incidence of cancer has shown an increasing trend especially breast cancer in Guilan province(Behboodi and Kazem-Nejad et al.,2015).

Unfortunately, breast cancer is multifactorial (Nouri et al., 2008, Keihanian et al., 2010) Epidemiologic studies have shown that genetic factors and environmental glandular breast cancer may start or continue to be involved (Keihanian et al., 2010).Some of these factors are proven and reliable sources of medical records such as age, family history of breast cancer, etc. However, smoking and nutrition are still under investigation (Eleazaret al., 2015). Since many of these risk factors are modifiable, their frequency would be changed at the society level via interventions.

Iran is located in the eastern mediterranean region (EMR) which its population, cultures, religious, habits, and knowledge of women differs from the women lived in developed countries. Differences in cultures, habits, and ethnicity affect on disparity in marital age, pregnancy features, age of menarche, and other important risk factors of breast cancer in this region. Having knowledge about risk factors of breast cancer in EMR can help policy makers to plan preventive strategies to reduce the incidence of it (Namiranian et al., 2013).Reducing the prevalence of the genomic, modifiable , environmental and infectious risk factors for cancer in the population may decline the cancer risk.

The aim of this study was to determine the breast cancer influencing factors in women referred to health centers in Guilan province in 2015-2016.

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Material and Methods

In a case- control study in 2014-2015, records of 262 patients with breast cancer registered in chemotherapy, radiotherapy and medical oncology centers over the past six years were collected from Razi Hospital in Guilan province. In fact, this Hospital is the only teaching hospital that has these sectors.

Via phone calls the all patients were informed about the purpose of the study and 225 patients were enrolled. For each case, one age-matched (group-matched) control was selected from a group of healthy women whose phone numbers were obtained from the patients. These people were not the patients' first or second- degree relatives, who preferably were not afflicted with cancer and age-matched subjects were ± 5 years old (Shrubsole et al., 2009) (Figure 1).

Data collection tool was questionnaire which were completed by the researcher after obtaining the verbal consent of participants .It was compiled based on several study tools (Eleazar et al.,2015).In our study content validity ratio (CVR) for all questions was also higher than 0.7 , according to the expert numbers in our study that was 10, numerical values of the Lawshe table was 0.62. In relation to the three parts of content validity index (CVI) all questions simplicity, clarity and relevance gained more than 0.7. All of responses' case group were related to before breast cancer.

The first part, clinical Personal Information, was similar in both groups. It included previous record of disease, drug use and hospitalization. The second part of the questionnaire included disease characteristics in case group (diagnostic method, duration of breast cancer, current treatments, age at diagnosis and disease status) and record ofhealthy behaviors in both groups (breast examination, mammography and ultrasound).

The third questionnaire consisted of non-modifiable risk factors (age, a family record of breast cancer and other cancers, age at men-arche,menopausal statusand a history of benign lumps).The fourth part included (physical activity ;at least 30 minutes a day, 3 times a week;, breastfeeding (history and duration), parity, age at first pregnancy, the number of children,abortion, irregular menstrual periods andmarital status). The fifth part of the questionnaire contained modifiable risk factors that are associated with an increased risk of breast cancer. These include alcohol consumption, smoking and its duration, exposure to X-Ray, rural residence, history of hormone replacement therapy(HRT),oral contraceptive pill (OCP) use (history and duration), postpartum mastitis, exposure to radiation and diet based on the food frequency questionnaire (FFQ). Frequency of each food item consumption was considered for one year (once a day, 4-2 times a day, 5-4 times a day, once-twice a week, 4-3 times a week, 5-6 times a week, once a month or less, twice-three times a month and never). The amounts in this study are based on daily intake of food. To identify dietary patterns, the food items were classified into 6 groups. Food items were grouped based on their similarity and conformity to food nutrients in Iran (Ahmadniaet al., 2016).

Data were also collected in the field as well as smoking status. We considered smokers as those who smoked regularly for at least 1 year (Inumaru et al., 2012).

The collected data was analyzed by SPSS software version 22, using descriptive and inferential statistics. To compare the relationship between variables and breast cancer the chi-square test was used and odds ratios were calculated using univariate logistic regression and level of meaningfulness (significance level) was considered lower level of 0.05. To evaluate the potential of predictive variables associated with breast cancer, borderline variables with P-values of < 0.2 were added to multivariate linear regression models (adjusted OR; 95% CI).

Results

In this study, 450 women were included. The mean± SD of age were respectively 49.7±10 years in breast cancer cases and 47.5±9.7 years in control group (p=0.2).The highest proportion of patients (28 percent) was diagnosed with breast cancer between ages of 36-50. In this study 34.2 percent of breast cancer cases were diagnosed before menopause. Diagnosis method in 55.5 percent of cases was breast self-examination (BSE).About 10.2% of the patients and 12.4% of controls had been hospitalized. In 62.7% of cases and 88.3% of controls BSE was not performed. In addition to 88.4% and 89.9% of participants who didn't performed mammography in cases and controls group, respectively.Also ultrasound examinations were not conducted in 89.3% of cases and 85.3% of controls.

In the case of non-modifiable factors, significant difference were found between two groups in terms of family record of other cancers (p=0.001). In addition the risk of breast cancer raised in women who have a family record of other cancers (OR= 3.5; 95 % CI= 1.96-6.6) . (Table 1).

Regarding reducing breast cancer risk, there was a significant difference between cases and controls due to history of abortion (p=0.02), labor history(p=0.003) , having regular menstruation (p=0.03), first pregnancy at the age of 20-35 (p=0.003) and the total duration of

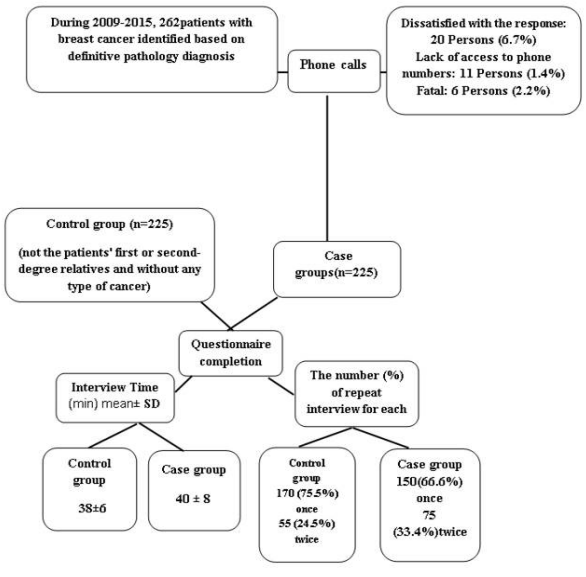

Figure 1. Flow Diagram of Samples

Table 1. Distribution of the Participants in Terms of Non-Modifiable Factors

Variables	Condition	Case n%	Control n%	P-value	Univariate OR(CI)
Age(yr)	20 - 30	1 (0.4)	8 (3.6)		1 (ref.)
	31 - 40	39 (17.3)	49 (21.8)	0.06	0.1 (0.009-1.1)
	41 - 50	87 (38.7)	82 (36.4)	0.5	0.6 (0.16-2.5)
	51 - 60	69 (30.7)	68 (30.2)	0.81	0.8 (0.2-3.2)
	61 - 70	24 (10.7)	14 (6.2)	0.76	0.8 (0.2-3.1)
	71 - 80	5 (2.2)	4 (1.8)	0.67	1.3 (0.3-5.2)
Family history of breast cancer	No	178 (79.1)	191 (84.9)		1 (ref.)
	Yes	47 (20.9)	34 (15.1)	0.11	0.6 (0.4-1.09)
Family history of other cancers	No	179 (79.6)	210 (93.3)		1 (ref.)
	Yes	46 (20.4)	15 (6.7)	0.001	3.5 (1.96-6.6)
Menarche(yr)	9 - 11	79 (35.1)	61 (27.2)		1 (ref.)
	12 - 14	67 (29.8)	87 (38.7)	0.28	0.5 (0.3-0.9)
	15 - 17	77 (34.2)	73 (32.6)	0.62	0.3 (0.5-1.2)
	18 - 20	2 (0.9)	4 (1.8)	0.39	0.2 (0.06-2.1)
Menopausal status	Premenopausal	102 (44.3)	110 (48.9)		1 (ref.)
	Postmenopausal	123 (55.7)	115 (51.1)	0.6	1.0 (0.8-1.2)
Age of Menopause	30 - 40	11	13		1.0 (ref.)
	40 - 50	87	70	0.87	1.1 (0.4-2.8)
	51 - 60	25	32	0.13	1.6 (0.8-2.9)

OR(CI), odds ratio(confidence interval 95%); ref, reference; P-values<0.05 significance

Table 2. Distribution of the Participants According to Reducing Modifiable Risk Factors

Variables	Condition	Case n%	Control n%	P-value	UnivariateOR(CI)
Education	Illiterate	66 (29.3)	29 (12.9)	0	1.0(ref.)
	Primary	96 (42.7)	74 (32.9)	0.001	5.4 (2.8-11.2)
	Secondary	46 (20.4)	81 (36)	0.001	3.1 (1.6-5.9)
	University	17 (7.6)	41 (18.2)	0.35	1.3 (0.7-2.6)
Marital status	Never	9 (4.0)	14 (6.2)		1.0 (ref.)
	Married	216 (96.0)	211 (93.8)	0.28	1.6 (0.7-3.7)
Physical activity	Not Everyday	148 (65.8)	130 (57.8)		1.0 (ref.)
	Everyday	77 (34.2)	95 (42.2)	0.08	1.4 (0.9-2.1)
Regular menstruation	No	88 (39.1)	21 (9.3)	0.03	1.0 (ref.)
	Yes	137 (60.9)	204 (90.7)		0.7 (0.4-0.9)
Parity	Nulliparous	21 (9.3)	40 (17.8)		1.0 (ref.)
	Parous	204 (90.7)	185 (82.2)	0.009	0.4 (0.3-0.8)
No of children	0	21 (9.3)	40 (17.8)		1.0 (ref.)
	1-3	150 (66.7)	144 (64)	0.02	1.9 (0.1-3.7)
	>4	54 (24.0)	41 (18.2)	0.007	2.6 (1.2-4.8)
Age at first pregnancy	<20	112 (53.1)	137 (67.1)		1.0 (ref.)
	20-35	94 (44.5)	66 (32.4)	0.003	1.8 (1.2-2.6)
	>36	5 (2.4)	1 (0.5)	0.09	2.3 (0.7-5.1)
History of breastfeeding	No	34 (15.1)	48 (21.4)		1.0 (ref.)
	Yes	191 (84.9)	176 (78.6)	0.08	0.6 (0.4-1.1)
Total duration of breastfeeding (months)	0	34 (15.1)	48 (21.3)		1.0 (ref.)
	1-6	8 (3.6)	90 (40.0)	0.001	0.3 (0.2-0.5)
	7-12	8 (3.6)	14 (6.2)	0.001	0.03 (0.01-0.1)
	>12	175 (77.8)	73 (32.4)	0.002	0.2 (0.1-0.6)
History of abortion	No	155 (68.9)	176 (78.1)		1.0 (ref.)
	Yes	70 (31.1)	49 (21.9)	0.02	0.7 (0.4-0.9)
Number of Abortion	1-2	218 (28.4)	219 (19.2)		1.0 (ref.)
	2-4	7 (3.1)	6 (2.7)	0.7	1.1 (0.3-3.5)

OR(CI), odds ratio(confidence interval 95%); ref, reference; P-values<0.05 significance

Table 3: Distribution of the Participants in Terms of Modifiable Factors Increase Risk

Variables	Condition	Case n%	Control n%	P-value	Univariate OR(CI)
History of Consumption alcohol	No	224 (99.6)	223 (99.1)		1.0 (ref.)
	Yes	1 (0.4)	2 (0.9)	0.56	2.0 (0.2-22.0)
History of HRT	No	208 (92.4)	202 (89.8)		1.0 (ref.)
	Yes	17 (7.6)	23 (10.2)	0.3	0.7 (0.3-1.3)
History of OCP use	No	135 (60)	141 (62.7)		1.0 (ref.)
	Yes	90 (40)	84 (37.3)	0.56	0.9 (0.6-1.3)
Total duration of OCP use(yr)	0	135 (65)	142 (63.1)		1.0 (ref.)
	1 - 8	43 (19.1)	64 (28.4)	0.006	0.2 (0.1-0.6)
	8 - 16	29 (12.9)	15 (6.7)	0.001	0.1 (0.0-0.5)
	> 16	18 (8)	4 (1.8)	0.1	0.4 (0.1-1.4)
Benign lump	No	200 (90.9)	220 (97.8)		1.0 (ref.)
	Yes	20 (9.1)	5 (2.2)	0.002	4.4 (1.6-11.9)
History of X-rays	No	215 (95.6)	201 (89.3)		1.0 (ref.)
	Yes	10 (4.4)	24 (10.7)	0.01	2.5 (1.1-5.5)
History of CT-scan	No	214 (95.1)	218 (96.9)		1.0 (reference)
	Yes	11 (4.9)	7(3.1)	0.3	1.6 (0.6-4.2)
Location	Urban	120 (53.3)	130(58)	0.34	1.0 (ref.)
	Rural	105 (46.7)	95(42.4)		1.1 (0.8-1.7)
"Frequency of milk and dairy use (glass)"	< 2a	110 (48.9)	136 (60.4)	0.9	1.0 (0.5-1.8)
	2 - 3b	34 (15.1)	26 (11.6)	0.2	0.6 (0.4-0.9)
	> 3c	81 (36)	63 (28)		1.0 (ref.)
"Frequency of meat and its derivatives use promise)	< 2a	39 (17.3)	60 (26.7)	0.001	0.5 (0.3-0.8)
	2 - 3b	60 (26.7)	53 (23.6)	0.001	0.4 (0.3-0.7)
	>3c	126 (56)	55 (24.4)		1.0 (ref.)
"Frequency of bread and cereals se(promise)"	<6a	151 (67.1)	145 (64.4)	0.02	0.4 (0.2-0.8)
	6-11b	26 (11.6)	43 (19.1)	0.37	0.8 (0.9-1.3)
	> 11c	48 (21.3)	37 (16.4)		1.0 (ref.)
"Frequency of vegetables use (promise)"	< 3a	24 (10.7)	71 (31.6)	0.03	0.5 (0.3-0.9)
	3 -5b	28 (12.4)	35 (15.6)	0.001	0.2 (0.1-0.3)
	> 5c	173 (76.9)	119 (52.9)		1.0 (ref.)
" Frequency of fruitage use (promise)"	< 2a	123 (54.7)	140 (62.2)	0.04	1.5 (1-2.2)
	2 - 4b	22 (9.8)	25 (11.1)	0.9	1.0 (0.5-1.9)
	> 4c	80 (35.6)	60 (26.7)		1.0 (ref.)

OR(CI), odds ratio(confidence interval 95%); ref, reference; OCP, oral contraceptive pill; HRT, hormone replacement therapy; a, Less than the amount recommended in the food pyramid per unit; b, The recommended food pyramid per unit; c, More than recommended in the food guide pyramid unit

breast-feeding (p<0.001). Therefore risk of breast cancer increased in women with a parity more than 4times and first pregnancy at the age of 36 (Table 2).

In regard to modifiable risk factors that are associated with an increased risk of breast cancer, Table 3 shows that there was a significant difference between the two groups concerning use of OCP for 1-8 years (p=0.006) and more than 16 years (p=0.001)and having history of X-ray (p=0.01).

In multiple linear regression analysis of higher education (OR=0.16;95%;CI= 0.03-0.77), using contraceptives for more than 16 years (OR=2.3.;95%; CI= 1.4-3.9), family history of other cancers (OR=6.1;95%;CI= 1.9-19.3) and a history of X-Ray exposure (OR=4.4;95%;CI= 1.07-18.1) were considered as predictive factors.

Discussion

The present study shows that educational level, family history of other cancers, age at first pregnancy, history of X-rays, number of children and inadequate intake of fruit are risk factors for breast cancer in Guilan; parity, regular menstruation, duration of breastfeeding, abortion, duration of OCP use, intake of meat, its derivatives, vegetables, inadequate intake of bread and cereals were protective against breast cancer.

In this study the mean age of cases was 49.7±10.0 years. Also the mean age of them at time of diagnosis was 48.3 ±10.1 years, which is same in different studies in Iran(Yavari et al., 2005, Hosseinzadehet al., 2014, Behboodi et al 2015)and other countries (Tazhibi et

al.,2014, Ahmed et al., 2015).

Mammography, as a screening test, is effective for early detection of the cancer (Berg et al., 2012). It is necessary to do regular periodic examinations and mammography in women, especially menopausal ages (Andrews et al., 2016). Unfortunately 88.4% and 89.9% of participants who didn't performed mammographyin cases and controls group respectively. That this issue can be linked to younger age of our sample's research.

In our study marital status have not appeared as a major factor for breast cancer. This findings are supported by different studies (Mohaghegh et al., 2014, Ahmedet al., 2015).

In this study, people withprimary, secondary and university levelsof education the risk of breast cancer were by 5.4 ,3.1 and 1.3 times , whereas with an decrease in the level of education, the breast cancer risk also increased. Some studies have suggested that educational level is associated with an in¬creased breast cancer risk (Braaten et al., 2004, Vidarsdottir et al.,2008, Hosseinzadeh et al., 2014), but many studies have found no association between breast cancer risk and the education level of individuals (Tehranian et al.,2009, Adib et al., 2012). Hereditary forms of breast cancer constitute only 5% to 10% of breast cancer cases overall (Apostolou and Fostira 2013, Economopoulouet al., 2015, Lincolnet al., 2015).

Similar to Omranipour et al.,(2015) study the result of present research wasn't found significantly association between breast cancer risk and family record of breast cancer, but this result is conflicted by other ones (Tehranian et al., 2009, Adib et al., 2012, Gathani et al., 2014, Ahmed et al., 2015).On the other hand, the risk of breast cancer in women with a family record of other cancers was three and half times higher than those who did not. Saki et al showed a significant difference between the two groups concerning a family record of other cancers and so it was considered a risk factor (2011).

Reproductive factors associated with prolonged exposure to endogenous estrogens, such as early menarche, late menopause, late age at first childbirth are among the most important risk factors for breast cancer (Zhanget al., 2012, WHO 2015).Collaborative Group on Hormonal Factors in Breast Cancer in a large pooled analysis of data from 117 studies, including 118,964 women with breast cancer (cases) and 306,091 without the disease (controls), found that for every year younger a woman was when she began her periods, her breast cancer risk increased by 5 percent (2011). In our study age at menarche was found no significant; the results were similar Omranipour, Mahmoodzadeh et al. 2015). The findings of our study indicate that people with regular menstruation cycles than those with irregular menstruation cycles, the risk of breast cancer,was reduced by 34 percent, the results were similar Saki et al., (2011).Parity protects women against the development of hormonally responsive breast cancer, and the earlier the first full-term birth occurs, the greater the protection (Britt et al., 2007).The present study indicates that increasing parity reduced the risk of breast cancer by 60%.Consistent with this, in a review study, the authors also concluded that increasing parity was associated with a pronounced decrease in the risk of breast cancer with each additional birth conferring a 10 percent risk reduction (Lambe et al., 1996).

A Systematic Review and Meta-Analysis has shown that the having first child after age 30years increases the risk of breast cancer by 48 percentin the EMR (Namiranian et al.,2013). In our study in comparison those who had aged at pregnancy under 20 years old, the age of the first pregnancy between 20-36 and more than 36 years old increases the risk of breast cancer by 1.8 and 2.3 times respectively, although it was only sig¬nificant in the univariate model in 20-36 years old .It should be noted that age of the first pregnancy more than 36 years old were recorded in a very low number of women (less than 1% in both case and control groups).In the end similar to studies' Hosseinzadeh et al., (2014) and Hadjisavvas et al. (2010).

we did not show a statistically significant association of late pregnancy with breast cancer in the final model. In our study, the history of abortion reduced the risk of breast cancer by 34%.Some previous studies suggested that abortion were associated with breast cancer (Hosseinzadeh et al., 2014, Mohaghegh et al., 2014).but not all of them (Karimet al.,2014, Borghesanet al.,2016). In our study with an increasing number of children, the risk of breast can¬cer raised;; however, there was no potential predictive variable for breast cancer risk. Some studies have found that increasing the number of pregnancies decreases breast cancer risk in women (Hadjisavvas et al.,2010, Keihanian, et al.,2010, Hosseinzadeh et al., 2014).In our study risk of breast cancer in women who had 1-6 months, 7-12 months and more than 12 months of breastfeeding reduced by 71 , 97 and 77 percent in comparison those who had never experienced. Some research also showed an association between breast cancer and duration of breastfeeding, a reduction of 66.3% was seen in cases with 12-23 months of breast-feeding and a decrease of nearly 87.4 percent for cases with 24 months or more (Franca-Botelhoet al., 2012). According to Tahrgorabyet al., (2014) the 3.4% reduction in the risk of breast cancer for every 12 months of breastfeeding reveals a clear protective effect.

Similarly to this study, other studies have not found an association between oral contraceptive use and cases of breast cancer (Sharifzadeet al.,2011, Karimet al., 2014), but Prolonged use of OCP (more than 16 years) was considered as predictive factors, this is consistent with a study in Saudi women (karim et al., 2014).

There is a strong evidence that physically active women have a lower risk of developing breast cancer than inactive women (Kruk and Czerniak 2013).According to reported Baglietto et al., the incidence of breast cancer among less physically active women was 40% higher than that in women who had higher rates of physical activity (2011). Surprisingly, the association between physically active women and breast cancer risk in the present study was increased by 40 percent, but this comparison is not significant. In another study in Iran, they did not show any significant relationship between physical activity and breast cancer (Hosseinzadeh et al., 2014). It seems that the definition and viewpoint of physical activity in our region differs from the other studies which may probably have been influenced on our findings in comparison to others.

Moreover, risk of breast cancer was increased in those

history of exposure X-Ray by 2.5 times rather than without history of exposure. Like the present research, studies have also shown that exposure to X-rays can increase the risk of breast cancer and are considered as non-modifiable factors (Omranipouret al.,2015). In our study, rural life increased the risk of breast cancer by 10 percent, but this comparison is not significant. Breast cancer shows a large urban-rural disparity worldwide (Hampton et al., 2008, Zhang et al.,2013). Fathi Najafi et al, examined risk factors of breast cancer in 350 women of childbearing age in Mashhad, there was a significant difference between most cases were in urban area and breast cancer (2005). In addition to other study also have pointed out that the breast cancer incidence was significantly higher in urban than in rural regions (Fei et al., 2015).Our results have suggested an association of dietary factors with breast cancer. We have explained these in our previous article (Ahmadnia et al.,2016).

Since our finding in both case and control groups about alcohol and smoking use were less than 1% we prefer not discuss them here.

One of the limitations of this study was persuading people to do telephone interviews which required more time and a good verbal communication.In addition, most of the data were obtained from the women's self-reports, therefore participants' memory and honesty were another limitations of this study especially in the case group.

The results of this study underlines the importance of informing women, particularly those at higher risk of breast cancer about risk factors, seeing as some of these risk factors are preventable. In addition, the results of this study emphasize the importance of informing women about breast cancer risk factors, particularly those at higher risk. So, identification of these risk factors are required as important means of prevention and treatment of breast cancer.

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