ORIGINAL ARTICLE

Identify Prognostic Risk Factor of Breast Cancer in North West of Iran

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ABSTRACT

Introduction: Breast cancer is the most common cancer and it is the second leading cause of cancer mortality for women after lung cancer in Iran. Given the high prevalence of breast cancer, it is of crucial importance to determine reproductive risk factors of breast cancer. **Methods:** A total of 139 female patients suffering from breast cancer (the case group) and 279 healthy females (the control group) who were age-matched participated in the study over the period from March 2018 to March 2019. Demographic and reproductive variables, including the number of pregnancies, breastfeeding, history of oral contraceptive use, abortion history, age at first menstruation and age at first childbirth, were all recorded via survey. Conditional Logistic regression was employed to calculate OR (CI: 95%). **Results:** The mean age of breast cancer patients was 50.8 ± 8.31. First degree family history of breast cancer, History of oral contraceptive use and delaying first pregnancy drastically increased the chance of breast cancer whereas breastfeeding and menstruation after the age of 14 reduced the chance of breast cancer. **Conclusion:** The findings of this study reveal that the age at first birth, use of oral contraceptives, first degree family history of breast cancer and lack of breastfeeding have a significant relationship with breast cancer. Thus, women who have experienced such factors are susceptible to breast cancer and need to be prioritized for preventive treatments and screening.

Keywords: Breast cancer; Breastfeeding; Abortion; Age at first pregnancy

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INTRODUCTION

Cancer is one of the most important causes of mortality and disability around the world(1). The high mortality rate of this disease in the past decade has caused the healthcare systems to devote rapt medical and caring attentions to fight this malignant disease(2). Based on the latest estimations by the International Agency for Research on Cancer (IARC), 1.25 million new cases of breast cancer are diagnosed throughout the world every year, with Iran having 8000 new cases per year(3, 4). Moreover, the IARC has predicted that this amount will reach 2.5 million annual cases in 2020(5). The prevalence of this disease is considerably higher in developed countries than it is in underdeveloped and developing countries(6, 7). The 5-year rate of survival for this type of cancer is 83% in developed countries and 53% in developing countries as the chance of earlier diagnosis and identification of the real cause is much higher in developed countries(8). After cardiovascular diseases and accidents, cancer is the third cause of mortality in Iran(9). Following skin cancer as the most common type of cancer, breast cancer is the second most prevalent type of cancer among Iranian women(10). This cancer is also the second cause of mortality among cancer patients after lung cancer(11). The mortality rate of breast cancer rose from 0.96 in 2003 to 4.33 in 2009 per 100000 population in Iran; likewise, the prevalence rate of this disease moved from 16 in 2003 up to 28.3 in 2009 per 100000 population(12). The results of different investigations regarding the prevalence rate in various geographical locations and emigrating populations have revealed that the prevalence rate in emigrant population becomes similar to the host population after one or two generations, proving the role of environmental factors in contracting breast cancer. Such findings support the hypothesis that reproductive factors together with other factors related to the lifestyle are the main variables in getting breast cancer(13, 14). The age-specific prevalence rate of breast cancer differs in various areas, and the mean age of breast cancer patients is 55 in developed

countries. Having the lowest mean age of breast cancer in the Middle East, Iranian patients have the mean age of 50 or less for breast cancer(15). Anything that increases the risk of cancer is defined as a risk factor. However, in contrast to many factors, immutable risk factors such as age, sex, race, first degree family history of breast cancer, etc., factors such as obesity, lifestyle, alcohol and tobacco use, estrogen consumption and history oral contraceptives have been called corrective risk factors. (14). Reproductive factors such as noli parietitis, old age at the time of first delivery and lack of breastfeeding are risk factors for breast cancer and play an important role in increasing breast cancer in women(16). The reason for an increase in the prevalence rate and a decrease in the mean age of this disease is probably the change in reproductive behaviors and lifestyles. Some studies have reported positive relationships between reproductive behaviors and the risk of breast cancer(17-19). Given the increasing number of instances of breast cancer in the past two decades in Iran and lack of ample information on the role of different, determining variables in the region, this study aims to determine reproductive risk factors of breast cancer in northwestern Iran.

MATERIALS AND METHODS

Study Design

This is a case-control study conducted from March 2018 to March 2019 in one of the most important cancer hospitals in northwestern Iran. A total of 140 female patients as the case group (new cases in the study period) and 280 healthy women (as the control group) regarding to the 1:2 matched who were age-matched participated in the study. Two incomplete and distorted checklists (one from each group) were excluded to guarantee the sufficiency of data for the analyses. Therefore, 139 and 279 individuals were included for the case and control groups respectively.

Subjects

The case group included those patients who were recently diagnosed with breast cancer in a cancer hospital in northwestern Iran. Pregnant women and women with previous breast cancer history who were receiving their routine treatments were not included in the study (use new case to control recall bias). As for each patient in the case group, two healthy (without breast cancer according to pathological results) females were selected in the control group in accordance with one female in the case group. The individuals in the control group were selected from the population of the patient's companion who were at the same age and were not from family members. The participants in the control group were individually age-matched with the case group (age at cancer diagnosis ± 3 years) and were interviewed at roughly the same time. In order to match the participants' age, those women who were suitable for the case group in terms of their age were selected; thus, the sampling in this study was done based on the convenience sampling method. Finally, a total of 279 healthy women who were age-matched with the case population were chosen as the control group. The statistical analyses were blinded in this study, the statistician believed that this is a primary analysis of an unfinished and ongoing sampling set of data.

Ethics

This study was confirmed by the Ethics Committee of Medical Science University (IR.ARUMS.REC.1398.349). All the participants volunteered to be involved in the study and made assured that their information would be kept secret.

Data Collection

Face-to-face interviews were conducted by four trained interviewers to collect the required data. The data were collected by a survey including questions regarding age, marital status, the number of children, first degree family history of breast cancer, having diseases other than cancer, breastfeeding, history of oral contraceptive use, nipple discharge, taking medication for other diseases, Body Mass Index (weight in kilogram divided by the square of height in meters), history of anemia, history of abortion, age at first menstruation and age at first childbirth.

Statistical Analysis

The frequency and percentage of categorical variables and the mean and standard deviation (SD) for all the continuous variables were calculated. To compare variables in the case and control groups, the Chi-square test was run for categorical variables, and independent samples t-test was used for continuous variables. In order to determine risk factors associated with breast cancer, the conditional logistic regression (estimate OR and 95% CI) was employed. All the significant factors in the univariate conditional logistic regression were entered in the multivariate conditional logistic regression model. The following variables were classified into two categories as either 'yes' or 'no': having diseases other than cancer, taking medication for other diseases, first degree family history of breast cancer, breastfeeding, History of oral contraceptive use, nipple discharge, history of anemia and history of abortion: the OR was calculated in comparison to the 'no' category. The number of pregnancies was classified into 'none', 1-3 and > 3: the OR was calculated in comparison to the 'none' category. The BMI was classified into < 18.5, 18.5-25, 25-30 and > 30: the OR was calculated in comparison to Normal BMI (18.5-25). Age at first menstruation was classified into < 14 and > 14: the OR was classified in comparison to < 14. Age at first childbirth was classified into < 23, 23-29 and > 29; the OR was calculated in comparison to < 23. The significant level was two-side and 0.05 in this study, and SPSS 22 software was used to run the statistical tests.

RESULTS

The age range of women suffering from breast cancer (the case group) was 27-68 with the mean age of 50.8 and SD of 8.31. The age range of women in the control group was 23-75 with the mean age of 49.6 and SD of 9.23. Hence, there was no significant difference between the two groups in this regard (P = 0.219). 92.8% of women in the case group and 91% of women in the control group were married (P = 0.431). The rest of the descriptive information is listed in Table I.

Based on the results of univariate conditional logistic regression, it was observed that those women who had a first degree family history of breast cancer were 5.71 times (95% CI:3.52-9.24), those who did not experience breastfeeding to their children were 2.22 times (95% CI:1.41-3.51), those who took oral contraceptives were 7.80 times (95% CI: 4.46-13.63), those who experienced nipple discharge were 6.38 times (95% CI: 3.59-11.34) and those who had the history of anemia were 3.60 times (95% CI: 1.20-10.74) more susceptible to the risk of contracting breast cancer. Women who experienced their first menstruation before the age of 14 were 1.75 times more prone to get breast cancer, compared to those who experienced it after they were 14 years old (95% CI: 1.17-2.85). Against to below 23 years mothers with delivery, women who gave birth to their first child within the age range of 23-29 were 2.05 time more (95% CI: 1.25-3.36) in risk of breast cancer. The odds ratio of cases with birth after 30 years was 12.97 (95% CI: 5.99-28.06) than those before they were 23 years old. The results show that other variables, including the number of pregnancies, having diseases other than cancer, taking other medications, history of abortion and BMI, were not related to breast cancer (Table II).

Table I: The frequency distribution of variables in the case and control groups

Factors	Category	Case Number (%) N=139	Control Number (%) N=279	P value
Age	$\bar{x}$ ±SD range	50.8±8.31 27-68	49.6±9.23 23-75	0.255 [b]
Number of pregnancies	$\bar{x}$ ±SD	3.07±1.38	3.19±1.47	0.483 [b]
Having diseases other than breast cancer	Yes No	48(34.5) 91(65.5)	94(33.7) 185(66.3)	0.883 [a]
taking medication for other disease than breast cancer	Yes No	31(22.4) 112(80.6)	49(17.6) 230(89.6)	0.001 [a]
First degree family history of breast cancer	Yes No	21(15.1) 118(84.9)	29(10.4) 250(89.6)	0.099 [a]
Breastfeeding	Yes No	73(52.5) 66(47.5)	192(68.8) 87(31.2)	0.001 [a]
Use of oral contraceptives	Yes No	110(79.1) 29(20.9)	100(35.8) 179(64.2)	<0.001 [a]
nipple discharge	Yes No	61(43.9) 78(56.1)	35(12.5) 244(87.5)	<0.001 [a]
History of Anemia	Yes No	129(93.5) 9(6.5)	271(98.2) 5(1.8)	0.001 [a]
History of Stillbirth	Yes No	1(0.7) 138(99.3)	4(1.4) 273(98.6)	0.001 [a]
Body Mass Index	$\bar{x}$ ±SD	26.68±3.70	26.2±3.69	0.0.279 [b]
Age at first menstrual period	$\bar{x}$ ±SD	15.00±2.75	15.71±2.58	0.027 [b]
Age at first birth	$\bar{x}$ ±SD	22.20±4.34	21.86±4.36	0.466 [b]

[b] Obtained from paired t-test for continuous variable and [a] obtained from McNemar Test for categorical variables

DISCUSSION

Breast cancer is a complex, multifactorial disease which has posed a serious threat to public health. Various factors are at play in the contraction and development of this type of cancer. These factors differ from one region to another. The current study centered on the relationship between reproductive factors and breast cancer in northwestern Iran. The findings of this study reveal that first degree family history of breast cancer, history of oral contraceptive use, nipple discharge and history of anemia are significant risk factors for breast cancer. On the other hand, breastfeeding, experiencing the first menstruation when 14 or above and the first childbirth when 23 or under are the protective factors against breast cancer.

The mean age and SD of breast cancer patients was 50.8 ± 8.31 so that 56% of patients were above 50 years of age. In the same vein, Trieu et al. reported that the mean age of breast cancer patients in their study was 49.2(20). This finding is in agreement with another study conducted in the north of Iran by Farahnaz et al. in which they observed that the mean age was 49.7, and 56% of the patients were 50 years old or older (21). Similarly, Alim et al. observed that the mean age of breast cancer patients was 51.8, and around 57% of the patients were above 50 years of age(22). With increasing age, the risk of breast cancer increases and most of the registered cases belong to the age group of 50-41 years (23).

The age at first menstruation was the other significant variable and those women who experienced their first menstruation when they were 14 years old or younger were 1.81 times more susceptible to getting breast cancer, in line with the findings of other studies (19, 22, 24). Post puberty Estrogen level increase in the blood. Therefore, premature menstruation causes the breast to be more and more exposed to estrogen and progesterone in the menstrual cycle and increase the risk of breast cancer (25).

Another significant variable was the age at first pregnancy; it is observed that women who had their first pregnancy at the age range of 23-29 were 2.11 times and those who had it above the age of 30 were 12.04 times more at risk of getting breast cancer, compared to those who experienced their first pregnancy at the age of 23 or younger. This finding is also corroborated by some previous studies (21, 26, 27). Another important factor among the risk factors for breast cancer is maternal age in the first pregnancy leading to live birth with full

Table II: Association between Breast Cancer and potential risk factors using Conditional Logistic regression (odds ratio)

Factors	Category	Case Number (%) N=139	Control Number (%) N=279	Unadjusted odds ratio (95% CI)	Adjusted odd ratios (95% CI)
Number of pregnancies	0(single)	8(5.9)	23(8.4)	1	
	1-3	74(54.4)	127(46.2)	1.66(0.70,3.92)	
	4-5	54(39.7)	125(45.5)	1.28(0.54,3.04)	
Having diseases other than breast cancer	No	91(65.5)	185(66.3)	1	
	Yes	48(34.5)	94(33.7)	1.04(0.68,1.56)	
taking medication for other disease	No	112(80.6)	230(82.4)	1	
	Yes	27(19.4)	49(17.6)	1.14(0.66,2.0)	
First degree family history of breast cancer	No	53(38.1)	218(78.1)	1	1
	Yes	86(61.9)	61(21.9)	**5.71(3.52,9.24)***	**2.54(1.32,4.85)***
breastfeeding	No	66(47.5)	87(31.2)	1	1
	Yes	73(52.5)	192(68.8)	**0.45(0.28,0.71)***	**0.37(0.18,0.76)***
Use of oral contraceptives	No	29(20.9)	179(64.2)	1	1
	Yes	110(79.1)	100(35.8)	**7.80(4.46,13.63)***	**3.90(1.97,7.70)***
nipple discharge	No	78(56.1)	244(87.5)	1	1
	Yes	61(43.9)	35(12.5)	**6.38(3.59,11.34)***	**2.55(1.24,5.26)***
History of Anemia	No	9(6.5)	5(1.8)	1	1
	Yes	129(93.5)	271(98.2)	**3.60(1.20,10.74)***	5.22(0.77,35.14)
History of Stillbirth	No	138(99.3)	273(98.6)	1	
	Yes	1(0.7)	4(1.4)	2.02(0.22,18.26)	
Body Mass Index	Normal (18.5-25)	74(57.8)	165(60)	1	
	Under (<18.5)	12(9.4)	24(8.7)	1.19(052,2.71)	
	Over (25-30)	31(24.2)	52(18.9)	0.89(0.42,1.89)	
	Obese (>30)	11(8.6)	34(12.4)	0.64(0.24,1.70)	
Age at first menstrual period	<14	53(38.1)	71(25.4)	1	1
	≥14	86(61.9)	208(74.6)	**0.57(0.36,0.86)***	0.51(0.25,1.01)
Age at first birth	<23	40(29.4)	164(59.6)	1	1
	23-29	49(36)	95(34.5)	**2.05(1.25,3.36)***	1.41(0.73,2.72)
	≥30	47(34.6)	16(5.8)	**12.97(5.99,28.06)***	**7.21(2.79,18.62)***

*Statistically significant(P<0.05), Unadjusted odd ratios (95% confidence interval): obtained from univariate conditional logistic regression, Adjusted odd ratios (95% confidence interval): obtained multivariate conditional logistic regression

gestational age. The link between childbirth and breast cancer is very complex, due to the interruption in estrogen synthesis and its termination during pregnancy, which prevents the proliferation of estrogen cells and can have a protective effect against breast cancer (28). The history of anemia was the other variable significantly related to breast cancer as women suffering from anemia were 3.78 times more likely to get breast cancer. This finding is in accordance with the findings of another study (29).

One previous study observed that the family history of cancer could increase the chance of breast cancer by 6.1 times(21). Likewise, it was observed in this study that women with the first degree family history of breast cancer were 5.79 times more prone to contract breast cancer. About 5-10 percent of breast cancer cases in women are caused by inherited mutations in cancer-prone genes such as BRCA1 and BRCA2, and the risk for women with mutations in the BRCA1 and BRCA2 genes is reported to be 60 and 85 percent, respectively (23).

Moreover, women who breastfed their children were 2 times less likely to have breast cancer, as also reported by some other studies (30, 31). Decreased chances of breast cancer in women with a history of breastfeeding may be due to changes in the physical tissue of the breast that are associated with milk production and prevent ovulation by altering the secretion of ovarian and pituitary hormones (32).

Some study showed that using oral contraceptives could raise the chance of getting breast cancer by about 100% (33). This issue has also been reported by other studies(34, 35). Also, the results of this study show that taking oral contraceptives may increase the likelihood of getting breast cancer by 6 times. Estrogen is the most important hormone, and exposure to it increases the risk of breast cancer and directly stimulates breast tissue and its cells. Androgens indirectly affect breast tissue by aromatizing to estrogen, especially in menopause (28).

Nipple discharge was also another significant variable, and the results of this study demonstrate that women experiencing nipple discharge were 5 times more susceptible to getting breast cancer as also observed in some previous research (36, 37). Nevertheless, the other variables of the study (i.e. having a disease other than cancer, using medication for other diseases and number of pregnancies) were not significantly related to breast cancer. Other studies have not found any significant relationships between these variables and breast cancer, either (19, 22, 33, 38).

Some of the limitation of this study are this study includes only those patients who were diagnosed with breast cancer within the time period of the study; thus, it was impossible to include more patients. This study is a retrospective study and according to the nature of such studies, it may suffer from recall bias in spite of the fact that the participant patients were not aware of

the relationship between reproductive factors and breast cancer. Therefore, it can be argued that the measurement error is quite random and similar in both groups. To overcome the recall bias, the questions were designed in a very understandable, clear format so that patients could easily understand them. Besides, ample time was given to the participants to answer the questions. Only one woman (0.7%) in the case group and 4 women (1.4%) in the control group had experienced abortion, hence the removal of this variable from the study.

One of the main advantages of this study is that the participants in the case and control groups were age-matched. The other advantage is the use of new cases in the case group to avoid recall bias.

CONCLUSION

The results of this study show that delaying first pregnancy, use of oral contraceptives, first degree family history of breast cancer and lack of breastfeeding have a significant relationship with contracting breast cancer. Women who have experienced the above-mentioned issues run the risk of getting breast cancer and need to be prioritized for preventive and screening treatments.

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