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ORIGINAL ARTICLE

# Breast Cancer Risk Factors in a Defined Population: Weighted Logistic Regression Approach for Rare Events

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**Purpose:** This study aimed to determine out risk factors for female breast cancer in a low socioeconomic population in Iran. **Methods:** Between 2007 and 2009, a total of 25,592 women who were ensured by the Imam Khomeini Relief Foundation participated in this screening program. The characteristics of patients diagnosed with breast cancer (n=111) were compared with those of control cases (n=25,481). In this study, we used relogit analysis (rare event logistic regression) with a weighting method using program Zelig. **Results:** Of 25,592 women, 3.9/1,000 had breast cancer, from which 38 were diagnosed during screening and 73 had already been diagnosed. The mean and standard deviation of age in breast cancer patients and in healthy controls were 49.18±8.86 years and 46.65±9.40 years, respectively. The findings based on the multivariate model revealed that the past history of ovarian cancer, hormone therapy, and first relatives with breast cancer were associated with increased risk for breast cancer. However, the use of oral contraceptive pills was found to be associated with reduced risk for breast cancer. **Conclusion:** Due to the rarity of the event in the population, relogit with a weighting method was used to investigate the major risk factors for breast cancer. These factors include oral contraceptive pill use, a history of ovarian cancer of the person under study, first relatives with breast cancer and hormone therapy.

**Key Words:** *Breast neoplasms, Logistic models, Risk factors, Screening program*

## INTRODUCTION

Breast cancer incidence and mortality varies more than 10-fold among different geographical areas. However, it is undoubtedly the most common malignancy in women [1] and ranks fifth as a cause of death due to its relatively good prognosis [2].

About half of breast cancer patients and 60 percent of its related deaths are estimated to occur in economically developing countries [3]. Breast cancer incidence has increased in Iran in recent years [4]. It has been reported that breast cancer is the most common malignancy amongst Iranian females [5]. According to a recent report, the estimated incidence of breast cancer was 22 per 100,000 in women aged 30 or more, and the prevalence was 120 per 100,000 [6]. Between 1998 and 2005, breast cancer survival showed an ascending trend in the country [6]. The breast cancer mortality rate has been reported to be 5.8 per 100,000 in 1998 and 2.5 per 100,000 for the female population in Iran in 2001 [7].

Breast cancer is seen mostly in adults over 50 years of age in Western countries, whereas a higher incidence rate can be seen in the age group of 40 to 49 in Iran [6]. The latest formal information of the age distribution of females with breast cancer in Iran shows the highest incidence among women 40 to 49 years of age (mean±standard deviation [SD], 48.4±12.5 years) [8].

Several epidemiological studies on risk factors for breast cancer have reported that breast cancer is related to family history of breast cancer, early menstruation, late onset of menopause, old age, age at first pregnancy over 30 years, infertility and not having children, use of contraceptives, hormonal treatment after menopause, no history of breastfeeding, overweight and obesity [9].

Although there have been substantial published studies on risk factors for breast cancer, population-based research is sparse, especially on low socioeconomic people in Iran. There-

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fore, we sought to determine risk factors for female breast cancer in a low socioeconomic population in Iran.

To estimate risks in observational studies, logistic regression models are often used, but in rare events, the estimates are biased and need correction [10]. At present, a screening program is performed on the apparently healthy population, and the number of cancer cases in a relatively large sample is also very low; thus, the disease is considered as a rare event. Logistic regression methods are not done with sufficient accuracy in determining risk factors. King and Zeng [10] conducted a two-state simulation study on rare events data using the usual logistic regression and weighted logistic regression, and then the results were compared. This study showed that weighted logistic regression led to coefficient and standard errors with less bias compared to logistic regression.

## METHODS

This screening population-based study was carried out to investigate risk factors for breast cancer between 2007 and 2009. A total of 27,008 women who were ensured by the Imam Khomeini Relief Foundation (IKRF) were recruited for participation in this study. From these women, 1,416 were lost during the study period.

Finally, a total of 25,592 women participated in the screening program, which comprises breast cancer cases (n = 111) and control cases (n = 25,481). All the participants were more than 30 years of age. IKRF was founded in Iran in 1980 for either to support the under-privileged and also to make them self-sufficient around the country. Women in this study were mainly from poor and low socioeconomic subgroups. In the present study, women were included from Tehran and other Iranian provincial capitals such as Shiraz, Mashhad, Kerman, Kermanshah, Bushehr, Qom, Isfahan, Gorgan, Rasht, and Yazd.

Ethical committee approval was obtained from Shiraz University of Medical Sciences before starting the study. All the subjects were first interviewed face to face for their general characteristics (age, educational level, marital status, occupation, socioeconomic status, and body mass index), menstrual and reproductive history (menopause, age at menarche, age at marriage, age at first pregnancy, number of pregnancies, and the use of hormone replacement therapy [HRT]) and first relatives as well as past history of breast and ovary cancer. Next, breast examination was done by a gynecologist or surgeon. All the participants in the age range of 35 to 60 years were then referred to the radiology center for mammography. For those above 60 or below 35 years of age, mammography was done according to the physician's opinion and the results of the breast examination. Breast cancer diagnosis was confirmed by biopsy.

When the sample is generated via a case-control design, we must correct for selecting on the dependent variable. While the slope coefficients are approximately unbiased, the constant term may be significantly biased. The weighing method is one of the correction methods performed in order to correct the case control design. Data are weighted by this procedure to make up for the differences in the prevalence of a disease in the sample and population. In the weighting method, the following weighted log-likelihood must be maximized to estimate the coefficients:

$$LnL_w(\beta|\gamma) = w_1 \sum_{\{Y_i=1\}} Ln\pi_i + w_0 \sum_{\{Y_i=0\}} Ln(1-\pi_i) = \sum_{i=1}^{n} \ln(1+e^{(1-2\gamma_i)\chi_i\beta})$$

$$w_i = w_1 y_i + w_0(1-y_i)$$

Where, $w_1 = \frac{\tau}{\bar{y}}$, $w_0 = \frac{(1-\tau)}{1-\bar{y}}$, $w_i = w_1\gamma_i + w_0(1-\gamma]$, $\bar{y}$ and $\tau$ are prevalence of a disease in the sample and population, respectively (the prevalence of breast cancer in the Iranian female population above 30 years of age is 120/100,000).

Two major problems that may restrict its application are as follows: firstly, computing standard errors on the basis of the information matrix is heavily biased. Secondly, the slope coefficient is biased in the sample of rare events data. The first problem could be easily solved by computing standard errors through white's heteroscedasticity-consistent variance matrix. With regard to the second problem, the biased-corrected estimate below should be used.

$$\tilde{\beta} = \hat{\beta} - bias(\hat{\beta})$$

Where, $bais(\hat{\beta}) = (x'wx)^{-1}x'w\xi$, $\xi_i = 0.5Q_{ii}[(1+w_1)\hat{\pi}_i - w_1]$, $Q_{ii}$ are the diagonal elements of $Q = x(x'wx)^{-1}$ and $w = diag\{\hat{\pi}_i(1-\hat{\pi}_i)w_i\}$ [10].

Statistical analysis was performed using statistical analysis software SPSS version 11.5 (SPSS Inc., Chicago, USA). Relogit (logistic regression model for rare events) analysis with a weighting method, which was performed using the program Zelig, was used to determine risk factors [11]. In the univariate model, odds ratios [ORs] and confidence intervals [CIs] were calculated. Covariates with a *p*-value of less than 0.25 were included into the multiple relogit model to determine risk factors.

## RESULTS

Of 25,592 women who participated in our study, 111 (411/100,000) women had breast cancer, from which 38 were diagnosed during screening and 73 were known cases. The

**Table 1.** Demographic results including chi-square test between case and control

| Variable | | Case (n=111) No (%) | Control (n=27,008) No (%) | *p*-value | Variable | | Case (n=111) No (%) | Control (n=27,008) No (%) | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Age (yr) | 30-39 | 18 (0.27) | 6,456 (99.72) | 0.03 | Age at first pregnancy (yr) | ≤18 | 44 (0.36) | 12,105 (99.64) | 0.43 |
| | 40-49 | 41 (0.42) | 9,770 (99.58) | | | 19-25 | 45 (0.47) | 9,452 (99.53) | |
| | ≥50 | 52 (0.56) | 9,221 (99.44) | | | ≥26 | 9 (0.46) | 1,965 (99.54) | |
| Marital status | Married | 21 (0.44) | 4,737 (99.56) | 0.66 | No. of pregnancies | 0-2 | 25 (0.35) | 7,018 (99.64) | 0.40 |
| | Single | 2 (0.40) | 501 (99.60) | | | 3-5 | 46 (0.45) | 10,130 (99.55) | |
| | Divorced | 26 (0.37) | 7,037 (99.63) | | | ≥6 | 39 (0.50) | 7,780 (99.50) | |
| | Widow | 61 (0.49) | 12,367 (99.51) | | | | | | |
| Occupation | Housewife | 97 (0.42) | 23,025 (99.58) | 0.09 | Hormone therapy | Yes | 31 (2.01) | 1,512 (97.99) | <0.01 |
| | Nonmanual | 10 (0.82) | 1,205 (99.18) | | | No | 80 (0.33) | 23,969 (99.67) | |
| | Manual | 4 (0.32) | 1,251 (99.68) | | | | | | |
| Educational level | Illiterate | 53 (0.56) | 9,345 (99.44) | 0.02 | OCP | Yes | 46 (0.35) | 13,098 (99.65) | 0.03 |
| | Primary school | 37 (0.32) | 11,514 (99.68) | | | No | 60 (0.53) | 11,273 (99.47) | |
| | High school -University | 19 (0.56) | 3,351 (99.44) | | | | | | |
| Body mass index | <25 | 21 (0.37) | 5,580 (99.63) | 0.13 | Ovary cancer | Yes | 9 (12.33) | 64 (87.67) | <0.01 |
| | 25≥, <30 | 41 (0.57) | 7,147 (99.43) | | | No | 102 (0.40) | 25,417 (99.60) | |
| | ≥30 | 23 (0.37) | 6,249 (99.63) | | | | | | |
| Menopause | Yes | 54 (0.58) | 9,243 (99.42) | 0.01 | First relative breast cancer | Yes | 12 (1.53) | 772 (98.47) | <0.01 |
| | No | 55 (0.34) | 16,028 (99.66) | | | No | 99 (0.40) | 24,709 (99.60) | |
| Age at menarche (yr) | ≤13 | 54 (0.42) | 12,921 (99.58) | 0.96 | First relative cancer | Yes | 24 (0.57) | 4,165 (99.43) | 0.13 |
| | ≥14 | 44 (0.42) | 10,421 (99.58) | | | No | 87 (0.41) | 21,316 (99.56) | |
| Age at marriage (yr) | ≤18 | 66 (0.39) | 16,839 (99.61) | 0.36 | First relative ovary cancer | Yes | 5 (1.88) | 260 (98.11) | <0.01 |
| | 19-25 | 34 (0.52) | 6,520 (99.48) | | | No | 106 (0.42) | 25,221 (99.58) | |
| | ≥26 | 4 (0.34) | 1,179 (99.66) | | | | | | |

OCP=oral contraceptive pill.

mean and SD of age of breast cancer subjects and healthy controls were 49.18±8.86 and 46.65±9.40, respectively.

The demographic and clinical features of the study population and the results of univariate relogit are shown in Tables 1 and 2, respectively. One factor gone through were at a higher risk in comparison with ones who still had menstruation ($p<0.01$). Breast cancer risk was significantly higher in woman with a past history of ovarian cancer, hormone therapy, and history of first relatives with breast or ovarian cancer. However, the use of oral contraceptive pills [OCPs] could lower the risk to approximately 66% ($p<0.01$). No significant differences were observed between cases and controls with regard to age, marital status, occupation, educational level, body mass index, history of cancer in first relatives, and reproductive factors.

Relogit analysis with a weighting method was performed for variables with a *p*-value of less than 0.25 on the univariate analysis. Eleven out of 16 variables were selected and taken into consideration in the multiple relogit model. The results of relogit analysis are described in Table 3. The findings from this study show that OCP use, positive history of ovarian cancer of the person under study, and positive familial background of breast cancer and hormone therapy could be predictors of breast cancer. By controlling the other factors, the probability of breast cancer among women with a positive history of ovarian cancer was nearly 24 times higher than that of women with a negative history ($p<0.01$).

A similar association was observed between those women with a positive history of breast cancer in their family and the diseases increasing the risk of breast cancer (OR, 2.64; $p=0.01$). Moreover, positive history of hormone therapy increased the chance of getting breast cancer. In other words, the risk of disease among females with a positive history of hormone therapy was approximately 6 times more than those without a history ($p<0.01$). Compared with women who never used OCP, women who had taken OCP tended to have a lower risk of breast cancer (OR, 0.57; $p<0.01$). However, other variables did not reveal any significant association with breast cancer.

## DISCUSSION

Breast cancer is becoming more common around the world. In Iran, it is the most common cancer among women, and its incidence rate is rising. Early detection of breast cancer is critical in reducing the mortality rate and improving patient prognosis [12]. In Iran women instructed to do self-exam for pres-


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**Table 2.** Univariate relogit results

| Variable | | OR (95% CI) | *p*-value | Variable | | OR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| Age (yr) | 30-39 | 1 | | Age at first pregnancy (yr) | ≤18 | 1 | |
| | 40-49 | 1.42 (0.72-2.80) | 0.31 | | 19-25 | 1.31 (0.77-2.22) | 0.32 |
| | ≥50 | 1.89 (0.95-3.77) | 0.07 | | ≥26 | 1.47 (0.36-6.02) | 0.59 |
| Marital status | Married | 1 | | No. of pregnancies | 0-2 | 1.23 (0.62-2.44) | 0.55 |
| | Single | 0.90 (0.21- 3.85) | 0.88 | | 3-5 | 1.37 (0.69-2.74) | 0.37 |
| | Divorced | 0.83 (0.47-1.47) | 0.52 | | ≥6 | 1 | |
| | Widow | 1.11 (0.68-1.83) | 0.67 | | | | |
| Occupation | Housewife | 1 | | Hormone therapy | Yes | 6.36 (3.59-11.28) | <0.01 |
| | Nonmanual | 2.32 (0.64-8.38) | 0.20 | | No | 1 | |
| | Manual | 1.17 (0.50-2.74) | 0.71 | | | | |
| Educational Level | Illiterate | 1 | | OCP | Yes | 0.66 (0.52-0.85) | <0.01 |
| | Primary school | 0.57 (0.28-1.16) | 0.12 | | No | 1 | |
| | High school-University | 1.04 (0.49–2.29) | 0.87 | | | | |
| Body mass index | <25 | 1 | | Ovary cancer | Yes | 41.78 (19.10-91.40) | <0.01 |
| | 25≥, <30 | 1.46 (0.77-2.75) | 0.24 | | No | 1 | |
| | ≥30 | 0.97 (0.50-1.88) | 0.93 | | | | |
| Menopause | Yes | 1.70 (1.22-2.38) | <0.01 | First relative breast cancer | Yes | 4.43 (2.02-9.70) | <0.01 |
| | No | 1 | | | No | 1 | |
| Age at menarche (yr) | ≤13 | 1.02 (0.63-1.64) | 0.94 | First relative cancer | Yes | 1.49 (0.91-2.43) | 0.11 |
| | ≥14 | 1 | | | No | 1 | |
| Age at marriage (yr) | ≤18 | 1 | | First relative ovary cancer | Yes | 6.45 (1.12-37.26) | 0.04 |
| | 19-25 | 1.36 (0.75-2.46) | 0.31 | | No | 1 | |
| | ≥26 | 1.31 (0.42-4.07) | 0.64 | | | | |

OR=odds ratio; CI=confidence interval; OCP=oral contraceptive pill.

**Table 3.** Effects of multiple breast cancer risk factors, modeled with relogit analysis

| Variable | | OR (95% CI) | *p*-value |
|---|---|---|---|
| Age (yr) | 30-39 | 1 | |
| | 40-49 | 1.02 (0.42-2.45) | 0.97 |
| | ≥50 | 1.07 (0.33-3.45) | 0.91 |
| Occupation | Housewife | 1 | |
| | Nonmanual | 1.89 (0.56-6.37) | 0.30 |
| | Manual | 1.15 (0.31-4.22) | 0.83 |
| Educational Level | Illiterate | 1 | |
| | Primary school | 0.58 (0.25-1.35) | 0.21 |
| | High school-University | 0.89 (0.44-1.83) | 0.76 |
| Menopause | Yes | 1.23 (0.71-2.14) | 0.46 |
| | No | 1 | |
| OCP | Yes | 0.57 (0.44-0.72) | <0.01 |
| | No | 1 | |
| Hormone therapy | Yes | 6.321 (3.92-10.21) | <0.01 |
| | No | 1 | |
| Ovary cancer | Yes | 23.921 (14.57-39.24) | <0.01 |
| | No | 1 | |
| First relative cancer | Yes | 1.161 (0.70-1.91) | 0.56 |
| | No | 1 | |
| First relative breast cancer | Yes | 2.64 (1.24-5.60) | 0.01 |
| | No | 1 | |
| First relative ovary cancer | Yes | 1.72 (0.27-11.07) | 0.57 |
| | No | 1 | |

OR=odds ratio; CI=confidence interval; OCP=oral contraceptive pill.

ence of breast cancer in screening programs. In addition, doctors examine them. If they are found to be positive for breast cancer, they will be referred for mammography.

This population-based screening study comprised women aged 30 to 88 years old and was conducted in a low socioeconomic population. We aimed to investigate the importance of sociodemographic and reproductive risk factors in relation to breast cancer susceptibility among women who were ensured by the IKRF, in Iran. We were interested in this subject because breast cancer can be considered a rare event in population based screening, and the relogit analysis with a weighting method was more precise than logistic regression in estimating the coefficients. In the present study, among the evaluated relevant factors, four factors including positive history of ovarian cancer, hormone therapy, positive history of breast cancer in first relatives and no history of OCP use were found to be significant predictors of breast cancer risk in the multiple relogit analysis.

In our study, the results of relogit analysis showed that women with a past history of ovarian cancer are at a higher risk for breast cancer than those who lack such a history. This finding is accordance with Fletcher's study in which women who had been diagnosed with cancer of the ovary are more vulnerable to develop breast cancer than women without cancer [13].

In the present study, a positive family history of ovarian cancer was associated with increased risk of breast cancer in the univariate analysis. This finding corroborates the result of the study carried out by Rezaianzadeh et al. [4] in which they showed that a positive familial history of ovarian cancer plays an important role in the causation of the disease.

The findings presented here confirm that a positive familial history of breast cancer may increase the risk for breast cancer. This finding is in harmony with reports of the positive relation between family history and breast cancer risk by other investigators [14-16].

Contradictory results have been reported on the relationship between OCP use and breast cancer risk. Some previous studies suggested that the use of OCPs is associated with increased risk of breast cancer [17-19]. Conversely, other studies reported either decreased or no significant association between contraceptive use and breast cancer risk [14,15]. Yankaskas [17] from the United States revealed that the use of OCP has a significant effect on increasing the risk of breast cancer. In a hospital-based case control study [18], OCP use was observed to be associated with increased breast cancer risk among Turkish women. Similarly, in a study by Van Hoften et al. [19], women over 55 years of age on OCPs for more than 10 years were more likely to have increased breast cancer risk. However, the duration of OCP use was not significantly related to breast cancer. As opposed to these findings, Ozmen et al. [9] suggested that the use of OCP could be a protective factor for breast cancer. Similarly, OCP use was found to be associated with decreased breast cancer risk among women within the age range of 30 to 75 years residing in an urban area of Yazd province of Iran. In that study, OCPs use decreased the probability of getting cancer down to 18% [20].

In our study, women with a history of using OCPs had a lower risk than that of women without it. Our finding is in line with other studies [19,20], but different from others [17-19]. However, later we realized that duration of use of OCP could be a factor. Therefore, further studies are required to elucidate the effect of duration of use of OCPs.

Our study confirmed that hormone therapy raised the chance of getting breast cancer. This finding is in accordance with some studies showing women with a history of HRT are more likely to have increased breast cancer risk [18,21]. Furthermore, in a meta-analysis of 51 epidemiologic studies, Lee et al. [22] reported that menopausal estrogen-progestin therapy resulted in a 7.6% increase in breast cancer. Conversely, in a university hospital-based nested case control study in Turkey, no association was found between HRT and breast cancer [9]. Therefore, similar to our study, the majority of the studies identified HRT as a significant predictor of breast cancer.

Our study revealed that menopause was associated with increased risk of breast cancer in the univariate analysis. Similarly, some previous studies suggested that postmenopausal women were at a higher risk compared to premenopausal women [17].

No significant association was observed between breast cancer and the other variables, which was an unexpected finding. For example, some previous studies have shown that there was a significant association with old age and increased risk of breast cancer [9,23].

In conclusion, breast cancer was considered as a rare event in this screening program. As a result, relogit with a weighting method was used to investigate risk factors for breast cancer. It can be concluded that the role of past history of ovarian cancer, positive history of breast cancer in first relatives, hormone therapy and no history of OCP use were more important than reproductive factors in a low socioeconomic population in Iran.

Finally, one should be aware of the limitation of this study as the results cannot be generalized. We investigated risk factors of breast cancer in a low socioeconomic population in Iran, therefore, some known risk factors may differ in the general population of Iranian women.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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