# Breast Cancer Risk Factors among Women without Family History in North West of Iran

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**Abstract:** Breast cancer is the most common cancer among Iranian women. This study aimed to investigate risk factors for non-familial breast cancer in the northwest of Iran. A case-control study was conducted from March 2010 to March 2012 in Tabriz, Iran. Two hundred women with breast cancer and 200 age-matched healthy women were included. Demographical data and risk factor related information were collected using a short structured questionnaire. Statistical analysis was carried out using conditional logistic regression with the forward elimination method and odds ratios (ORs) with related 95% confidence intervals (CIs) were estimated. The mean ± SD ages of cases and controls were 50.05±11.47 and 49.91±11.83 years, respectively. Multivariate analysis showed that low to moderate socioeconomic status (OR=6.19, 95%CI: 2.92-13.11), previous genital surgery (OR=3.97, 95%CI: 1.53-10.33) and no history of miscarriage (OR=2.41, 95%CI: 1.14-5.09) were risk factors for breast cancer. These findings indicate that low to moderate socioeconomic status, previous genital surgery and no history of miscarriage are factors significantly associated with increased breast cancer risk among Iranian women within Northwest of Iran.
[Pourzand A, Farajkhah H, Azhough R, Fakhree MB. **Breast Cancer Risk Factors among Women without Family History in North West of Iran**. *Life Sci J* 2013;10(7s):482-489]. (ISSN:1097-8135). http://www.lifesciencesite.com. 75

**Keywords:** Breast cancer; case-control study; risk factors; Iranian women

## 1. Introduction

Breast cancer (BC) is the second most common type of cancer and the leading cause of cancer death in women worldwide (Parkin et al., 2005). During the last decades, the changes in human lifestyle have caused to increase the incidence and prevalence rate of breast cancer and different risk factors in the world (Fredslund and Bonefeld-Jørgensen, 2012). There are significant variations between geographic areas regarding breast cancer incidence, with higher rates in developed countries and lower rates in developing countries (Bagchi, 2008) including Iran.

Cancer is a major public health problem in Iran and breast cancer ranks first among cancers diagnosed in women (Sadjadi et al., 2005). Several studies have indicated that the age of breast cancer patients in Iran are 10 years younger compared to developed countries (Harirchi et al., 2000). In addition, the majority of patients in Iran present with disease at advanced stages (Harirchi et al., 2009).

Numerous epidemiological studies on risk factors of breast cancer have produced evidence on international variations. Studies have identified several variables as risk factors for breast cancer in women, including a family history of the disease, age, reproductive factors (early age at menarche, <12 years; late age at menopause, >54 years; nulliparity; late age at first full term pregnancy, >30 years), high mammographic breast density, higher hormone levels, race, economic status, ionizing radiation in childhood, lifestyle, diet, weight, alcohol intake and smoking (Möller et al., 2003; Yavari et al., 2006; Bernstein, 1998; Boyd et al., 1995). However, 75% of women who are diagnosed with BC have no risk factors (Amir et al., 2010), and it is not possible to identify specific risk factors in the majority of cases (Lacey et al., 2009).

There are differences between sporadic and familial breast cancer including younger ages and worse prognosis for familial cases (Nordin et al., 2011). There are few studies about breast cancer risk factors in patients without family history of the disease. Several risk factors are considered for breast cancer, some of which are confirmed, while others are controversial and may be rejected in the future. In Iran, few studies about breast cancer risk factors exist, especially in patients without familial history. The aim of current study is to identify breast cancer risk factors in women with no family history of the disease in northwest of Iran.

## 2. Material and Methods

In this prospective case control study, 200 women with diagnosed breast cancer visiting Imam Reza and Shams Hospitals, Tabriz, Iran between March 2010 and March 2012 were included. For the control group, 200 women with similar sociodemographic characteristics as the case group were selected. Age was matched for both the case and control groups. Inclusion criteria for both groups

included age, being 20 years or older, and willingness to participate and no history of breast cancer in their family. The exclusion criteria for control group were previous diagnosis of BC or any other malignancies, gynecological problems (e.g., artificial menopause by hysterectomy), pregnancy, endocrine problems, and psychological conditions (dementia or schizophrenia). During the study period, breast cancer cases (n=232) that fulfilled the above criteria were approached while waiting for their oncologist appointment and were given an introductory letter outlining the goals of the study. Among them, 200 patients agreed to participate in this study as the case group. Written consent was signed by each case and verbal agreement for interview participation was obtained for each control subject.

Researchers contacted the subjects, both the cases and the control group, at the hospital and administered questionnaires for data collection. Demographic and risk factor data were collected from both cases and controls with the use of a specially designed questionnaire, through a standardized interview. The questionnaire included information on age, marital status, level of education, current BMI, exercise status, smoking status (i.e. never, past, current smokers), family history of breast cancer (i.e. first degree relatives), use of hormone replacement therapy and a range of reproductive characteristics such as age at menarche, number of pregnancies, gestation period, parity, overall duration of breastfeeding, use of oral contraceptives, age at first and last pregnancy (at the beginning of the term). Other than BMI (which was based on actual measurements of weight and height), all other factors investigated here, were self-reported.

All data were analyzed using SPSS statistical package version 16.0 (SPSS Inc. Chicago, IL, USA). Continuous data with normal distribution are given as mean ± standard deviation, otherwise as median. The chi-square test was used in the statistical analyses to evaluate the significant factors associated with breast cancer risk. Logistic regression was used to construct a multivariate model of independent factors associated with increased breast cancer risk. Forward stepwise regression was used for factor selection. For each factor in the model, the likelihood of breast cancer risk was estimated by the odds ratios and 95% CI. A *P* value of 0.05 or less was considered significant.

## 3. Results

Demographic characteristics of cases and controls were similar between two groups. The mean age of cases and controls were 50.05±11.47 and 49.91±11.83 years, respectively (*P*= 0.9). There was no difference between cases and controls in weight (71.19±13.05 vs. 69.64±9.75; *P*=0.17) and height (15.99±0.68 vs. 16.11±0.57; *P*=0.06). Mean body mass index (BMI) was significantly higher in cases in comparison to controls (27.87±5.06 vs. 26.82±3.49; *P*=0.001). Sociodemographic characteristics of cases and controls are shown in Table 1. Patients with breast cancer were significantly more obese (*P*=0.001), had lower income (*P*<0.001) and higher history of genital surgery (*P*=0.009) and previous breast cancer (*P*<0.001).

Table 2 indicates reproductive history and menstrual factors among cases and controls. Patients with breast cancer had significantly earlier menopause (*P*=0.006) and less miscarriage (*P*=0.01). There was also a tendency to have older age at menarche, at first live birth and at last live birth in patients with breast cancer.

We evaluated some other potential risk factors for breast cancer (Table 3). There was significant differences between groups in eye color (*P*<0.001), skin color (*P*=0.002) and hair form (*P*=0.03); as breast cancer cases significantly had brown eyes, dark skin and smooth blonde and smooth brown hair. Patients with breast cancer also significantly had higher history of radiation (*P*=0.01), less brassier use (*P*=0.01), less or no use of mobile (*P*=0.03), and more worried or nervous (*P*<0.001) and mostly had B type personality (*P*<0.001).

Variables with significant difference between cases and controls were further evaluated by multivariate logistic regression analysis to define factors associated with breast cancer risk (Table 4). Among these, three factors were found to be associated with breast cancer risk as statistically significant independent factors; including low to moderate socioeconomic status as the strongest (OR=6.19, 95%CI: 2.92-13.11). The other two were previous genital surgery (OR=3.97, 95%CI: 1.53-10.33) and no history of miscarriage (OR=2.41, 95%CI: 1.14-5.09).

## 4. Discussion

In this case controls study among women without family history of breast cancer in Northwest of Iran, we found three modifiable risk factors for breast cancer including lower socioeconomic status (as the strongest risk factor), history of any kind of genital surgery, and no history of miscarriage.

The role of some risk factors for breast cancer has been investigated in our country in the recent years. Various risk factors have been studied among Iranian women population: family history and marital status (Ebrahimi et al., 2002; Naieni et al., 2007; Yavari et al., 2005), body mass index, higher education (Naieni et al., 2007), late menopause (Naieni et al., 2007; Motie et al., 2011), late age at

first birth (Yavari et al., 2005; Hajian-Tilaki and Kaveh-Ahangar, 2011), history of abortion, nulliparity (Naieni et al., 2007; Hajian-Tilaki and Kaveh-Ahangar, 2011), number of live births, and use of oral contraceptive pills (Motie et al., 2011).

**Table 1.** Sociodemographic characteristics of cases and controls (* *P* value is two tailed significant)

| | | Cases N (%) | Controls N (%) | P value |
|---|---|---|---|---|
| age | ≤39 years | 35 (17.5) | 36 (18) | 0.99 |
| | 40-49 years | 73 (36.5) | 73 (36.5) | |
| | ≥50 years | 92 (46) | 91 (45.5) | |
| Residence | Urban | 182 (91) | 189 (94.5) | 0.24 |
| | Rural | 18 (9) | 11 (5.5) | |
| Marital status | Single | 11 (5.5) | 8 (45) | 0.88 |
| | Married | 177 (88.5) | 178 (89) | |
| | Divorced | 3 (1.5) | 4 (2) | |
| | Widowed | 9 (4.5) | 10 (5) | |
| Age at marriage | ≤20 years old | 104 (55) | 85 (45) | 0.08 |
| | >20 years old | 88 (45.8) | 104 (54.2) | |
| Education | Illiterate | 31 (15.5) | 24 (12) | 0.52 |
| | Primary and middle school | 68 (34) | 69 (34.5) | |
| | High school | 64 (32) | 60 (30) | |
| | College+ | 37 (18.5) | 47 (23.5) | |
| Body mass index | 19-24.9 (normal) | 57 (28.5) | 59 (29.5) | 0.001* |
| | 25-29.9 (overweight) | 76 (38) | 106 (53) | |
| | ≥30 (obese) | 67 (33.5) | 35 (17.5) | |
| Job | Housewife | 149 (74.5) | 156 (78) | 0.46 |
| | White collar | 38 (19) | 29 (14.5) | |
| | Blue collar | 13 (6.5) | 15 (7.5) | |
| Night worker | Never | 193 (96.5) | 188 (94) | 0.44 |
| | 0-1 per week | 0 | 2 (1) | |
| | 2-3 per week | 6 (3%) | 8 (4) | |
| | 4-5 per week | 1 (0.5) | 2 (1) | |
| Socioeconomic | ≤ moderate | 129 (64.5) | 80 (40) | <0.001* |
| | > moderate | 71 (35.5) | 120 (60) | |
| Parents relationship | Cousins | 12 (6) | 13 (6.5) | 0.94 |
| | Far family | 8 (4) | 7 (3.5) | |
| | Not related | 180 (90) | 180 (90) | |
| Genital surgery | Yes | 47 (23.5) | 26 (13) | 0.009* |
| Physical exercise | No | 138 (69) | 151 (75.5) | 0.25 |
| | Less than 30 minutes/day | 27 (13.5) | 25 (12.5) | |
| | More than 30 minutes/day | 35 (17.5) | 24 (12) | |
| Smoking | No | 192 (96) | 196 (98) | 0.38 |
| | Yes | 8 (4%) | 4 (2%) | |
| Alcohol use | No | 199 (99.5%) | 198 (99%) | 0.9 |
| | Yes | 1 (0.5%) | 2 (1%) | |
| Previous breast disease | Yes | 17 (8.5%) | 2 (1%) | <0.001* |

Furthermore, having more episodes of full-term pregnancy, longer duration of breast feeding, and parity of two or more were shown to be protective factors for breast cancer (Naieni et al., 2007). We found no protective factor among our population. Positive family history was reported as risk factors among Iranian women in a few studies (Ebrahimi et al., 2002; Naieni et al., 2007); however, in order to reduce the possible effects of genetic heritance on other risk factors, we studied women without family history of the disease.

**Table 2.** Reproductive history and menstrual factors among cases and controls (HRT, hormone replacement therapy; * *P* value is two tailed significant)

| | | Cases N (%) | Controls N (%) | P value |
|---|---|---|---|---|
| Age at menarche | ≤12 years old | 42 (21) | 59 (29.5) | 0.06 |
| | >12 years old | 158 (79) | 141 (70.5) | |
| Menopause | Yes | 88 (44) | 80 (40) | 0.47 |
| | No | 112 (56) | 120 (60) | |
| Age at menopause | ≤45 years old | 24 (27.3) | 12 (15) | 0.006* |
| | 46-50 years old | 20 (22.7) | 36 (45) | |
| | ≥51 years old | 44 (50) | 32 (40) | |
| Weight gain after menopause | Yes | 32 (36.4) | 25 (31.3) | 0.51 |
| | No | 56 (63.6) | 55 (68.8) | |
| Parity | Nullipara | 10 (5.3) | 17 (8.9) | 0.15 |
| | 1-3 | 108 (57.1) | 118 (61.5) | |
| | ≥4 | 71 (37.6) | 57 (29.7) | |
| Age at first birth | ≤30 years old | 165 (92.2) | 166 (94.9) | 0.39 |
| | >30 years old | 14 (7.8) | 9 (5.1) | |
| Age at last birth | ≤30 years old | 92 (51.4) | 104 (59.8) | 0.13 |
| | >30 years old | 87 (48.6) | 70 (40.2) | |
| Breast feeding | Never | 35 (17.5) | 36 (18) | 0.26 |
| | <12 months | 59 (29.5) | 73 (36.5) | |
| | ≥12 months | 106 (53) | 91 (45.5) | |
| Miscarriage | No | 120 (66.7) | 94 (53.7) | 0.01* |
| | Yes | 60 (33.3) | 81 (46.3) | |
| Menstrual cycle | Regular | 157 (78.5) | 170 (85) | 0.12 |
| | Irregular | 43 (21.5) | 30 (15) | |
| HRT (after menopause) | No | 80 (90.9) | 75 (93.8) | 0.57 |
| | Yes | 8 (9.1) | 5 (6.3) | |
| Oral contraceptive use | No | 171 (85.5) | 176 (88) | 0.55 |
| | Yes | 29 (14.5) | 24 (12) | |

Breast cancer is usually considered as a disease of high socio-economic status (Krieger, 1990). In our study, there was no significant differences regarding educational status, however unlike usual concern, we found low monthly income (low socioeconomic status) as the strongest predictor of breast cancer. There is also controversy according to the effect of education on breast cancer. Previous studies have shown higher education (Naieni et al., 2007; Fujino et al., 2008) as the possible risk factor, whereas some studies (Ozmen et al., 2009; Lee et al., 2004) found that higher education was a protective variable for breast cancer. However, similar to our study, some other studies (Yavari et al., 2005; Motie et al., 2011) found no significant effect.

Smoking is a possible risk factor with controversial results; some studies have found positive results (Sezer et al., 2011; Baron et al., 1996), but other studies found no association (Lawlor et al., 2004). We did not find any study to report smoking as a risk factor among Iranian women. Similarly, this association was not observed in our study population. It is worth mentioning that smoking cigarette in Iranian females is not a prevalent finding.

Alcohol use is another approved risk factor of breast cancer (Lew et al., 2009). Alcohol consumption is so rare among Iranian females due to religious beliefs and social norms of our society. We found only three cases with history of alcohol consumption; alcohol was not considered as a risk factor on our study.

**Table 3.** Some other potential breast cancer risk factors (* P value is two tailed significant)

| | | Cases N (%) | Controls N (%) | P value |
|---|---|---|---|---|
| Eye color | Albino | 0 | 1 (0.5) | <0.001* |
| | Blue | 7 (3.5) | 3 (1.5) | |
| | Green | 5 (2.5) | 17 (8.5) | |
| | Gray | 5 (2.5) | 5 (2.5) | |
| | Brown | 172 (86) | 136 (68) | |
| | Black | 11 (5.5) | 38 (19) | |
| Skin color | Clear | 81 (40.5) | 115 (57.5) | 0.002* |
| | Dark | 118 (59) | 85 (42.5) | |
| | Black | 1 (0.5) | 0 | |
| Hair form | Smooth blonde | 15 (7.6) | 3 (1.5) | 0.03* |
| | Curly blonde | 3 (1.5) | 1 (0.5) | |
| | Smooth brown | 52 (26.3) | 45 (22.5) | |
| | Curly brown | 31 (15.7) | 42 (21) | |
| | Smooth black | 59 (29.8) | 70 (35) | |
| | Curly black | 38 (19.2) | 39 (19.5) | |
| Radiation | Yes | 12 (6) | 2 (1) | 0.01* |
| | No | 188 (94) | 198 (99) | |
| Brassier use | Not at all | 16 (8) | 6 (3) | 0.01* |
| | sometimes | 18 (9) | 7 (3.5) | |
| | ≤12 hours a day | 21 (10.5) | 44 (22) | |
| | 12-24 hours a day | 145 (72.5) | 143 (71.5) | |
| Mobile use | Not at all | 45 (22.5) | 29 (14.5) | 0.03* |
| | Sometimes | 57 (28.5) | 77 (38.5) | |
| | Everyday | 98 (49) | 94 (47) | |
| Computer use | Not at all | 140 (70) | 122 (61) | 0.12 |
| | Sometimes | 47 (23.5) | 65 (32.5) | |
| | everyday | 13 (6.5) | 13 (6.5) | |
| Psychological status | Calm | 52 (26) | 28 (14) | <0.001 |
| | Average | 42 (21) | 96 (48) | |
| | Worried | 65 (32.5) | 48 (24) | |
| | Nervous | 41 (20.5) | 28 (14) | |
| Personality type | Type A | 27 (13.5) | 70 (35) | <0.001* |
| | Type B | 152 (76) | 78 (39) | |
| | Borderline | 21 (10.5) | 52 (26) | |

**Table 4.** Independent factors associated with breast cancer risk (based on results of logistic regression model).

| Factors | Odds ratio | 95% Confidence interval | | P value |
|---|---|---|---|---|
| | | lower | upper | |
| Socioeconomic | 6.19 | 2.92 | 13.11 | <0.001 |
| Genital surgery | 3.97 | 1.53 | 10.33 | 0.005 |
| Miscarriage | 2.41 | 1.14 | 5.09 | 0.02 |

Increase in BMI is considered as a breast cancer risk factor in Iran (Naieni et al., 2007) and other countries (Key et al., 2003). Our results were in accordance with these studies. Physical activity is reported as a protective factor for breast cancer (Suzuki et al., 2008; Hellmann et al., 2010). However such a relationship was not observed in our study.

Association of reproductive factors and breast cancer is widely reported. The reported reproductive factors were late menopause, late age at first birth, history of abortion, nulliparity, number of live births and use of oral contraceptive pills (Naieni et al., 2007; Yavari et al., 2005; Motie et al., 2011; Hajian-Tilaki and Kaveh-Ahangar, 2011). There are also some established protective factors including earlier first birth, higher parity, and later age at menarche, having more episodes of full-term pregnancy, longer duration of breast feeding, and parity of two or more (Naieni et al., 2007; Colditz and Rosner, 2000). In our study, although women with breast cancer had earlier menopause and less miscarriage, only miscarriage was found as an independent risk factor.

There is some evidence in regard to association of a history of abortion with higher breast cancer in genetically susceptible women (Becher et al., 2003). Another study in Iran did not report abortion as a risk factor of breast cancer (Yavari et al., 2005). Unlike previous findings, having no history of abortion in our study was a significant risk factor for breast cancer. This difference between this study and other studies can be due to excluding women with positive family history, as abortion effects was previously reported in women with family history of the disease (Becher et al., 2003). However, these findings need to be confirmed in future studies.

Another significant risk factor of breast cancer in our study was previous history of any kind of genital surgery (diseases of uterus and ovary, e.g. endometriosis). The probability of the interaction between ovary and breast cancer has been studied previously. It was reported that endogenous hormones such as progesterone and adrenal androgens may play a role in breast cancer (Bernstein and Ross, 1993). This hormone alteration could be seen in some medical conditions like endometriosis and ovarian cysts, and their relationship to breast cancer has not been resolved (Moseson et al., 1993; Kelsey et al., 1993). Weiss et al. (1999) found no association between breast cancer risk and a history of surgery for endometriosis. Our results are debating the possible effect of genital disease and surgery history on breast cancer and thus women with surgery history should be evaluated and screened more cautiously.

There were number of limitations such as the small sample size and the selection of case and controls which may affect the interpretation of our results. Another limitation of the study is that all of the data was obtained from the women's self-reports and so some answers especially about early reproductive status could be unreliable. Intensive studies of breast cancer risk factors in developing countries might reveal other important risk factors in these populations. Findings of our study can be useful, as it was conducted in Iran – a developing country – which could be different from developed countries.

In conclusion, the results of this study show that low to moderate socioeconomic status, previous genital surgery and no history of miscarriage were associated with breast cancer risk factor among women in Northwest of Iran. More studies are recommended to explore the determinants of breast cancer in Iran.

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