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A Case-Control Study of Breast Cancer in Northeast of Iran: The Golestan Cohort Study

Sadaf Alipour, MD[1,2]; Ramesh Omranipour, MD[1,3]; Reza Malekzadeh, MD[4,5]; Hossein Poustchi, MD[6]; Akram Pourshams, MD, PhD[4]; Masoud Khoshnia, MD[4,7]; Abdolsamad Gharavi, MD[4,7]; Gholamreza Roshandel, MD, PhD[5,7]; Bita Eslami, PhD[1*]

[1]Breast Disease Research Center (BDRC), Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Surgery, Arash Women's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Surgical Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
[4]Digestive Disease Research Center, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[5]Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[6]Liver and Pancreatobiliary Disease Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[7]Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran

Abstract

Background: The incidence and survival of breast cancer (BC) vary across countries. This study aimed to determine risk factors for BC and estimate the overall survival rate in BC patients of the Golestan Cohort Study (GCS).

Methods: This case-control study was performed among participants of the GCS. Cases (N = 99) consisted of women who were diagnosed with BC and controls (n = 400) were selected out of women participating in the same cohort and had not developed any cancer during the follow-up period. Controls were frequency matched to case on both place of residency and 5-year categories of age.

Results: Considering confounding variables, logistic regression analysis manifested a reverse association between parity and BC (OR [odds ratio] = 0.87, 95% CI: 0.80–0.95, $P = 0.001$). In addition, we found women who had family history of any cancer (OR = 1.63, 95% CI: 1.02–2.60, $P = 0.04$) and long term oral contraceptive (OCP) use (≥10 years) (OR = 3.17, 95% CI: 1.27–7.95, $P = 0.01$) were at higher risk of BC. Of the total patients, 23 (23.2%) were died due to BC after a mean follow-up of 102.4 ± 5.31 months. Using the Kaplan-Meier analysis, the 5-year survival in these patients was 74%.

Conclusion: In the Golestan Cohort population, long term OCP use and family history of cancer were risk factors for BC, while parity was a protective factor. The 5-year survival of BC patients in the GCS is still lower relative to Europe and the United States.

Keywords: Breast cancer, Cohort study, Risk Factor, Survival analysis

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Introduction

According to estimates from the World Health Organization (WHO) in 2018, cancer is the second leading cause of death before 70 years of age in many countries, and its incidence and mortality are growing worldwide rapidly due to socioeconomic developments and changes in lifestyle.[1] Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer deaths in women. However, its prevalence and incidence vary across countries and within each country, depending on the degree of development as well as social and life style factors in the region.[2] Results from national death statistics of Iranian Ministry of Health and Medical Education shows the increasing trend of mortality in BC specifically for those aged between 15–49 in comparison with women older than 50 years.[3] Numerous studies have been performed to find the risk factors for BC in Iran,[4-9] but they have demonstrated inconsistent results.

Since prospective cohort studies are the best approach for reducing error and recall bias in evaluation of lifestyle related diseases,[10] and because there are limited data about risk factors for BC in Iran based on a large cohort study, this study was designed to evaluate BC in the Golestan Cohort Study (GCS) as the first large cohort study in northeastern Iran. The Golestan population based cancer registry (GPCR) showed that BC is the most common malignancy in Golestan females and is one of the major public health problems in that region.[11] Age-standardized incidence rate (ASR) of BC in females in Golestan province was reported to be 18.36 per 100 000 from the Iranian National Cancer registry in 2009.[12] However, another study in 2012 showed an ASR of 28 per 100 000 person-year in BC for Golestan province, with an unusual peak in young women of non-Turkmen ethnicity.[13]

The Breast Disease Research Center (BDRC) of Tehran University of Medical Sciences (TUMS) has joined the Golestan Cohort to identify risk factors for BC by comprehensive assessment of available information in the GCS.

*Corresponding Author: Bita Eslami, PhD; Breast Disease Research Center (BDRC), 2nd Floor, Sadaf Building, Imam Khomeini Hospital, Keshavarz Blvd., Tehran, Iran. Tel: +982161192761; Email: b-eslami@alumnus.tums.ac.ir

Material and Methods

Study Design and Participants

This study was a case-control study and the study population consisted of women enrolled in the GCS. In brief, a total number of 50 045 people aged 40–75 were recruited from inhabitants of the northeastern part of Iran (Gonbad city and villages from Golestan province) between 2004 and 2008. Trained interviewers gathered individual information by in-person interview. Depending on the participant's preference, they interviewed in local language (Turkmen) or in the country's national language (Persian). A general questionnaire included demographic characteristics, tobacco use, alcohol drinking, anthropometric measurement (height, weight, waist and hip circumferences), reproductive and medical history in participants and their relatives. Before interview, an informed consent was obtained from each participant. The total number of women who participated in GCS was 28 811 women, 21% (6064) from urban and 79% (22 747) from rural areas. All participants were followed up actively every year. The subjects were asked to contact the cohort team in the case of development of serious disease or hospitalization. Information obtained from these contacts are registered and followed up in order to detect relevant diseases. Meanwhile, data of Golestan cancer registry are also reviewed monthly to find new cancer cases among the study subjects that participants might have forgotten to report to GCS.

Cases and Controls Selection

One hundred twenty-six women with BC were found in the GCS. Twenty-seven women (21.4%) had BC history at time of entering the cohort, and BC developed in ninety-nine women (78.6%) during the follow-up period. Therefore, 99 cases were entered in our study as the case group.

Inclusion criteria for controls were: No diagnosis of BC or any other cancer except skin cancer until the final follow-up. Controls were frequency matched to cases of both place of residency and 5-year categories of age (41–50 to 71–75). Considering matching factors, four hundred controls were randomly entered into the study.

Risk Factors Evaluation

Available data related to BC and its possible risk factors (demographic, reproductive, past medical history, family history of any cancer and specifically BC, tobacco use, and oral contraceptive (OCP) use) were extracted from the Golestan questionnaire. Anthropometric indices such as weight, height, waist and hip circumferences were extracted, as well. The waist- hip ratio was calculated as waist divided to hip circumference. Body mass index (BMI) was calculated by the formula of weight divided by height squared (kg/m^2) and categorized based on WHO classification (<18.5, 18.5–24.9, 25–29.9, $\geq$ 30 kg/m^2).

Because only 5 women had university education, we have not established a separate group for this category and it was combined with the previous group. Therefore, we have four categories for education (illiterate, equal or then than 5 years, 6-8 years, and higher than 9 years).

Follow-up of BC Patients

All BC patients were followed-up. The information about the present status of patients (Death or Alive) and follow-up time was obtained from Golestan cancer data. Death due to BC was approved by reviewing the medical records and death certificate by GCS group.

Statistical Analysis

SPSS software (version 20, SPSS, Inc, IL, USA) was used for all statistical analyses. Results were presented as mean (standard deviation; SD) for continuous variables and frequency for categorical variables. Comparison of characteristics between cases and controls was done using chi-square test (χ^2) or Fisher exact test for categorical variables and student's t test for continuous variables. A two-sided P value less than 0.05 was considered significant.

Multivariable binary logistic regression (backward stepwise method) was used to estimate adjusted Odds ratio (OR) and 95% confidence interval (CI) for assessing the association between BC and risk factors. Age and place of residency were also included in the model as confounding factors. Final analysis was performed using parity (n), BMI (kg/m^2), family history of any cancer (yes/no), and duration of OCP consumption (non- user or less than 1 year, 12–48 months, 49–119 months, long-term user $\geq$10 years) in the model. Linearity assumption was checked for parity and BMI and linear relationship between continues independent variables and logit transformation of the dependent variable was confirmed. Variables were selected a priori for inclusion in multivariable models on the basis of association with BC in univariate analysis (P value < 0.2).

In addition, the overall survival of BC patients in this study was calculated considering the information about the present status of patients (death or alive) and follow-up time using the Kaplan-Meier method.

Results

Frequency matching resulted in comparable distributions of cases and controls by age and residency. Characteristics of cases and controls are presented in Table 1. Overall, BC patients, compared to the control group, had lower parity but stronger family history of cancer although the latter was marginally non-significant ($P = 0.059$). None of the participants in both groups reported alcohol consumption.

Table 2 shows the results of the binary logistic regression analysis of risk factors of BC and reports the crude and adjusted OR. Our analysis showed a reverse association between parity and BC (OR = 0.87, 95% CI: 0.80–0.95,

Table 1. Total Characteristics of the Case (Breast Cancer) and the Control Group

Variables	Case (n = 99)	Control (n = 400)	P Value
Parity (n)	5.10 ± 3.09	6.19 ± 2.96	0.001
BMI (kg/m²)	28.96 ± 5.40	28.14 ± 5.44	0.18
Waist/Hip ratio	0.94 ± 0.09	0.95 ± 0.09	0.58
Marital sStatus			
Single	1 (1)	2 (0.5)	
Married	85 (85.9)	340 (85)	0.37
Widow	11 (11.1)	56 (14)	
Divorced	2 (2)	2 (0.5)	
Education			
Illiterate	65 (65.7)	302 (75.5)	
Equal or less than 5 years	19 (19.2)	55 (13.8)	0.26
6-8 years	6 (6.1)	16 (4)	
Higher than 9 years	9 (9.1)	27 (6.8)	
Smoker	2 (2)	15 (3.8)	0.55
Family history of cancer	44 (44.4)	137 (34.2)	0.059
History of cancer in first degree relatives	28 (28.3)	84 (21)	0.14
Family history of breast cancer	4 (4.2)	8 (2)	0.24
OCP use	34 (34.3)	133 (33.2)	0.91
Duration of OCP use			
Non-user or less than 1 year	66 (66.7)	285 (71.2)	
12–48 months (1–4 years)	17 (17.2)	60 (15)	0.06
49–119 months	7 (7.1)	42 (10.5)	
≥10 years	9 (9.1)	13 (3.2)	
BMI category			
<18.5	1 (1)	14 (3.5)	
18.5–21.99	8 (8.1)	39 (9.8)	0.41
22–29.99	47 (47.5)	200 (50.1)	
≥30	43 (43.4)	147 (36.8)	

Data shown as mean ± SD and number with percentages in parenthesis.
P value refers to t test in comparison of continues variables and chi-square test or fisher exact test was conducted between categorical variables.
BMI, body mass index; OCP, oral contraceptive pills.

$P = 0.001$). In addition, we found women who had family history of any cancer (OR = 1.63, 95% CI: 1.02–2.60, P = 0.04) and long term OCP use (≥10 years) (OR = 3.17, 95% CI: 1.27–7.95, P = 0.01) are at higher risk of BC.

Evaluation of the present status of the BC patients shows 23 (23.2%) were dead due to BC after the mean

follow up of 102.4 ± 5.31 months. Figure 1 shows the overall survival rate of the GCS BC patients. Using the Kaplan-Meier analysis, the 5-year survival rate was 74% and the overall survival rate in the present study sample was found to be 61.4%.

Discussion

This case-control study in the GCS population showed that long-term OCP use (≥10 years) and family history of any cancer were risk factors for BC; whereas parity was a protective factor. Our result showed a 5-year survival rate of 74% for BC patients in GCS.

In this study, the women who had history of long-term OCP (≥10 years) use were at a higher risk of BC compared with the reference group (non-OCP users and less than 1 year users). However, we did not find any significant difference between the 2 groups in terms of OCP use (34.3% vs. 33.2%). Since some of these women had a history of OCP use of less than 1 year, we categorized OCP users based on duration of OCP use. The relationship between OCP and BC incidence is controversial in the related literature. Some researchers believe OCP is related to BC and many reject such a relationship. A recent study in 2018 evaluated the risk of BC and OCP considering BRCA1 and BRCA2 mutation carriers.[14] They concluded that OCP use and duration of usage were associated with BC risk in BRCA1 mutation carrier in cohort retrospective analysis. Meanwhile, OCP use and duration were related to BC in BRCA2 mutation carrier in prospective analysis. They revealed that OCP consumption could increase the risk of BC in women who had a genetic susceptibility. However, genetic evaluation was not performed in our patients and considering the results of interviews, there were no significant differences in number of cases and controls who reported a family history of BC (Table 1). The results of a recent study in 2018 showed that in the Indian population, a history of or current use of OCP increases the risk of BC (OR = 2.4, 95% CI: 1.2–5).[15] Another study in 2014 in USA compared recent OCP use with never or former use and reported that in women aged 20 to 49 years, recent use was associated with an

Table 2. Risk of Breast Cancer According to the Participants' Variables Using Logistic Regression Analysis

Variable	Crude OR (95%CI)	P Value	Adjusted OR (95% CI)	P Value
Parity (n)	0.88(0.81–0.95)	0.002	0.87(0.80–0.95)	0.001
Family history of cancer (yes/no)	1.54(0.98–2.40)	0.06	1.63(1.02–2.60)	0.04
OCP use				
Nonuser or less than 1 year	ref			
12–48 months (1–4 years)	1.22(0.67–2.23)	0.51	1.22(0.64–2.33)	0.55
49–119 months (5–9 years)	0.72(0.31–1.67)	0.45	0.76(0.32–1.80)	0.53
≥ 120 months (≥ 10 years)	2.99(1.23–7.29)	0.02	3.17(1.27–7.95)	0.01

OR, odds ratio; CI, confidence interval; OCP, oral contraceptive pill.
Parity, BMI, family history of any cancer, and duration of OCP consumption were entered to the model after controlling age and place of residency as confounding variables.
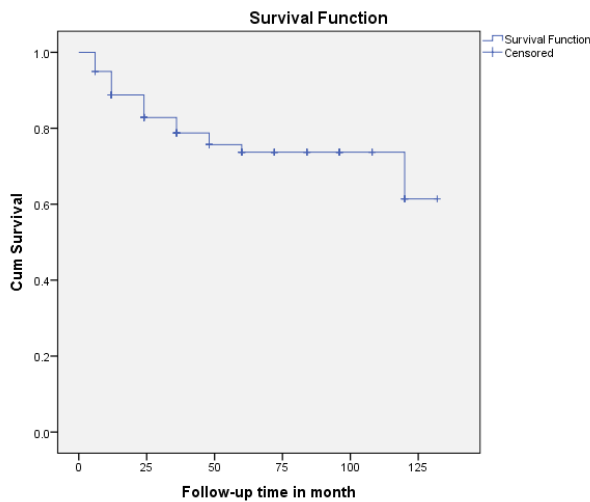
Figure 1. The Overall Survival in Breast Cancer Patients of the Golestan Cohort study (GCS).

increased risk of BC; this association was stronger in estrogen receptor positive (ER+) patients. [16] As well, data from the Global Epidemiology Study (GFS) in the United States revealed that OCP usage increased the risk of BC recurrence.[17] Two recent studies evaluated the association between duration of OCP use and risk of BC and didn't find any association between OCP use and BC with a large sample size.[18,19] However, in our study, the number of long-term OCP users in both groups was very low; this may have caused overestimated odds ratio. Therefore, more evaluation of the effect of OCP in long-term users is needed in a large scale study. Our findings about overall OCP use, as a risk factor of BC, are not equivalent to other studies conducted in different regions (Shiraz, Tabriz, and Urmia) of Iran.[4,7,8] Similar to the present study, the result of a study in Mazandaran province (north of Iran) did not represent OCP as a risk factor for BC.[6] The Nurse's Health Study cohort in the USA observed no overall relationship between OCP use and BC risk in women over 40 years of age.[20] On the other hand, some studies have reported a protective role for OCP in BC.[21] Our suggestion is that the effect of OCP on the risk of BC may be due to individual characteristics such as menopausal status, genetic mutations and environmental factors. Therefore, we propose that the relation of OCP and BC be evaluated in the context of a probable combined effect with above mentioned risk factors.

Along the same line, we found that family history of cancer increased the risk of BC with adjusted odds ratio equal to 1.63. Since GCS was designed with the aim of studying gastrointestinal (GI) cancers and most of the participants were low educated, the data regarding family histories of breast and especially ovarian cancer were not consistently investigated and documented. We therefore only included family history of any cancer in the analysis, which yielded a significant difference between the two

groups.

The result of the logistic regression analysis in our study showed the protective effect of multiparity on BC, as previously reported, in all ages.[22] A meta-analysis also confirmed that low parity is a significant and independent determinant of breast-cancer risk.[23] This result was represented in other investigations in our country as well.[5,7,22]

Previous studies in Iran reported the relationship between BC and education level.[6,7] Since the majority of women in GCS were illiterate or had lower education level, we couldn't find any relation between BC and education in this study. The explanation for these contradictions about the association between education level and BC may be that the relation is mostly due to other accompanying factors such as lifestyles, occupation, parity, and age at first pregnancy.

Table 3 shows a great difference in survival rates across the world that was reported in 2005. According to this study, the 5-year survival rate in the United States was 74% for black women vs. 89% for white women.[24] Meanwhile, the 5-year survivals in southern and central European countries were estimated at about 80% and lower in all eastern European countries (60–70%).[25] Based on Table 3, the 5-year survival in the GCS population is still lower than white women in the United States, southern and central European countries, and Australia.[24] On the other hand, the 5-year survival rate of this study was higher in comparison with eastern central countries (60-70%), Philippines (40.9%),[26] Thailand (63.7%),[27] and other developing countries (43-63%).[24] The 5-year survival rate of our study is similar to China between 1982–1991 (Shanghai, 72%)[28] and black women in the United States from 1995 to 2000 (74%).[24] We should mention that all of the above-mentioned studies were performed before 2000, and it is expected that developments in treatment of BC would be associated with an increase in survival rates over the world. Since the overall 5-year survival rate in Iran from 2001 to 2006 was 71% and it was reported to be 62%–69% in the northern part of Iran,[29] it seems

Table 3. The 5-Year Survival Rates of Breast Cancer in Some Countries

Country	Year	5-Year Survival Rate
Unites States		
Black women	1995–2000	74%
White women		89%
Southern & Central European countries	1990–1999	80%
Eastern European countries	1990–1999	60–70%
Australia	1988–1992	79%
China		
Shanghai	1988–1991	72%
Gidong	1982–1991	55.7%
India	1980s	45.1–55.1%
Philippine (Rizal province)	1983–1987	40.9%
Thailand (Chiang Mai)	1983–1992	63.7%
Present study	2004–2018	74%

that survival rates are increasing in Iran. However, early detection through screening strategies in order to increase survival rates in Iran is strongly recommended.

This study displayed various strengths. Firstly, in order to reduce errors and recall biases, we conducted this study considering data from the GCS, which is a large scale and valid prospective cohort study. The second advantage is that all participants were actively followed-up for a long time.

This study had some limitations. The first limitation was that data about reproductive history was insufficient. Secondly, the number of long-term OCP users was very low in both groups and this causes overestimation of odds ratio. Thirdly; since GCS was primarily designed to evaluate GI cancers, evaluation of family history of cancer mostly focused on GI cancers. Although the GCS team tried to report BC correctly, the diagnosis was based on the self-report of patients and some reported BC may have been benign that will increase the survival time of the patients.

In conclusion, evaluation of the GCS data manifested that long-term OCP use and family history of cancer are risk factors of BC; and multi-parity is a protective factor. In addition, we found a 5-year survival rate of 74% for BC in the GCS population, which is still lower than the United States and some European countries. Such findings may assist us in targeting susceptible women for prevention of BC as a major public health problem. Further evaluation regarding the risk factors of BC in the context of cumulative risk assessment of genetic and environmental factors in order to assist providers and stakeholders in taking actions to reduce the incidence of BC and increasing survival rates with screening strategies are needed.

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