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Relationship between Reproductive Factor and Breast Cancer in Mazandaran Cohort: A Case-Control Study

M. Moosazadeh (PhD)[1], R. Roohi [2], A. Hedayatizadeh-Omran (PhD)[2], M. Kheradmand (PhD)[1], Gh. Janbabai (MD)[3], R. Khazaei (MD)[4], R. Alizadeh-Navaei (PhD)*[2]

1.Health Sciences Research center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, I.R.Iran
2.Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, I.R.Iran
3.Tehran University of Medical Sciences, Tehran, I.R.Iran
4.Babol University of Medical Sciences, Babol, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Identification of cancer risk factors in the community and prevention planning in high-risk groups can be helpful in cancer prevention program. Hence, the aim of this study was to investigate the relationship between reproductive factors and breast cancer in the Tabari population-based cohort study in a case-control design.

METHODS: This case-control study was performed on the enrolment phase of the Tabari population-based cohort. Patients with breast cancer were considered as case group (51) and non-cancerous individuals (204) as a control group. The two groups were matched based on age category and oral contraceptive pill (OCP) intake. The studied variables included breast cancer history, demographic and reproductive factors.

FINDINGS: Mean age of first pregnancy (22.76±4.99 vs. 20.8±4.16, p=0.005), mean age at first birth (23.57±4.94 vs. 21.66±4.07, p=0.006) and age of marriage (22.24±5.75 vs. 19.54±4.92, p=0.001) in the case group were significantly higher than the control group and the number of pregnancies (3.76±2.22 vs. 4.67±2.76, p=0.032) and number of children (3.27±1.97 vs. 4.16±2.44, p=0.019) in the case group was significantly less than the control group. According to multivariate analysis, the odds of incidence of breast cancer in people with first pregnancy over 22 years was 2.76 times more than (p= 0.027) those with first pregnancy age below 22 years.

CONCLUSION: "Age at first full-term pregnancy" is one of the major risk factors for breast cancer in the area.

KEY WORDS: *Reproductive factor, Risk factors, Breast cancer, Persian cohort, Tabari cohort.*

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***Corresonding Author: R. Alizadeh-Navaei (PhD)**
Address: Gastrointestinal Cancer Research Center, Mazandaran University of Medical Sciences, Sari, I.R.Iran
Tel: +98 11 33257230
E-mail: reza_nava@yahoo.com

Introduction

Breast cancer is the most common cancer in women and the first cause of cancer death in women aged 40 to 44 years. This malignancy accounts for 33% of all female cancers and is responsible for 19% of all cancer-related deaths (1,2). Annually, 180,000 women are diagnosed with this cancer in the United States (3). Breast cancer is the most common cancer in Southeast Asia (4), and global statistics indicate an increase in the incidence of breast cancer and its rapid increase in developing countries. Currently, about one-third of all cancers in women in developing countries constitute breast cancer (5,6).

The epidemiological pattern of breast cancer in Iran is similar to that of Eastern Mediterranean and other developing countries (7). All women of all ages are at risk of developing breast cancer, but with age, the risk increases (8). However, the age of breast cancer in Iran is 15 years younger than in other countries (9). Breast cancer risk factors include a wide range of factors including age, gender, and family history of breast cancer, increased breast density, genetic susceptibility, and menarche before age 12, and normal menopause after 45 years. Risk of breast cancer is associated with a history of fertility, including having no fertility history or being old at the first pregnancy and replacing endogenous and exogenous hormonal factors, no breastfeeding, and infertility (10).

Increased exposure to exogenous estrogen and prolonged use of estrogen (over 5 years) during life are associated with an increased risk of breast cancer (11). Given that nearly a quarter of breast cancers are preventable (12), identifying risk factors in our community and planning for at-risk groups can be helpful in this regard. Considerable studies have been conducted on breast cancer risk factors within the country (13-15) and even in the province of Mazandaran in 2011 (16), all of which were hospital-based, with varying degrees of severity. And this is the first cohort study to examine this relationship in a population, and its control are from the community that are highly validated in these studies. The aim of this study was to investigate the relationship between fertility factors and breast cancer in the inclusion phase of the Mazandaran population cohort as a case-control design.

Methods

This case-control study was performed on the inclusion phase data of cohort study on Tabari population. The Tabari population cohort is part of a national mega cohort named Prospective Epidemiological Research Studies in Iran (PERSIAN), which is detailed in the published profile cohort (17,18). The code of ethics of the present study was IR.MAZUMS.IMAMHOSPITAL.REC.1397.3068.The age group of the Tabari cohort population is between 35 to 70 years. The population of women was 6106, of whom 51 had breast cancer. Breast cancer patients were considered as case group and those without breast cancer as control group. Due to the limited number of cases (n= 51), the sampling method was census and the controls were selected randomly.To increase the study power, the number of controls was selected four times more than case number.

Inclusion criteria were breast cancer in the case group and no breast cancer in the control group, then case and controls according to each age group 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-70 and OCP consumption (as one of the major risk factors for breast cancer) were matched. The number of cases and controls in the age group of 35-39 years were 5 and 20, respectively (out of 1021), the age group of 40-44 years, 2 and 8 respectively (out of 1062), and 45-49 years, 7 and 28 respectively (out of 1078), 50-54 years 9 and 36 respectively(out of 980), and 55-59 12 and 48 respectively (out of 869), and 60-64, 10 and 40 respectively (out of 647) and 65-70 years were 6 and 24 respectively (out of 398).

The variables studied were breast cancer, age, oral contraceptive use, body mass index, menstrual age, marriage age, gestational age, menopausal age, place of residence, marriage status, number of births, number of children, number of abortions, lactation history, duration of lactation and family history of breast cancer. Data were analyzed by SPSS software (version: 19). Comparison of grouped and quantitative variables between case and control groups was performed by Chi-square and independent t-test, respectively. Crude odds ratios for reproductive variables were also estimated using inter-logistic regression. Multivariate logistic regression test was used to adjust the effect of the variables suspected of blocking. Variables entered into the multivariate model

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include body mass index, education level, socioeconomic status, area of residence, diabetes and marital status, age at first complete pregnancy, lactation age, menarche age, age of menopause, number of pregnancies and history of abortion. Also, the significant level of the hormone therapy was 0.0001 and was not included in the model. $p<0.05$ was considered significant.

Results

The mean age of the case and control groups was 54.4±9.9 and 54.3±8.9 years, respectively. Among other demographic variables such as education level (p= 0.144), BMI (p= 0.512), area of residence (p= 0.413), socioeconomic status (p= 0.744), marital status (p= 0.495) , hormone therapy (p= 1), and diabetes (p= 0.558) were no significant difference between the case and control groups (Table 1).

Mean age of first pregnancy (22.76±4.99 vs. 20.8±4.16 with p= 0.005), mean age at first birth (23.57±4.94 vs. 21.66±4.07 with p= 0.006) and the mean age of marriage (22.24±5.75 vs. 19.54±4.92 with p= 0.001) were significantly higher in the case group and the number of pregnancies (3.76±2.76 vs. 4.67±2.76 with p= 0.032) and number of children (3.27±1.97 vs. 4.16±2.44 with p= 0.019) in case group was significantly less than the control group (Table 2).

The incidence of cancer in people with first pregnancy above 22 years old was 2.09 times higher than those with first pregnancy at age of 22 years and younger than 22 years (p= 0.026). The chances of developing breast cancer were 28% lower than those of nulliparous women (p= 0.671). The chance of developing breast cancer in people with lactation duration less than 11 months is 1.37 times higher than who had lactation duration more than 11 months or more. Also, the incidence of breast cancer in menarche younger than 13 years was 1.14 times higher in menarche at age of 13 years and older (p= 0.684) and in menopausal women over 46 years old was 1.55 times higher in women with menopausal age less than 46 years (p= 0.223). Also, the results of multivariate logistic regression test showed that the incidence of breast cancer in people with first pregnancy over 22 years is 2.76 (p= 0.027) times more than people with first pregnancy at 22 years or less than 22 years (Table 3).

Table1. Frequency distribution of underlying variables between breast cancer patients and healthy controls (control group)

Variable	Case (51 people)	Control (204 people)	P-value
Duration of Study			
Academic	(13.7) 7	(15.7) 32	
9 to 12 years	35.3) 18	(19.1) 39	0.114
6 to 8 years	(7.8) 4	(5.9) 12	
1 to 5 years	(23.5) 12	(27.5) 56	
illiterate	(19.6) 10	(31.9) 65	
BMI			
<25	(17.6) 9	(16.2) 33	0.512
25-29.9	(35.3) 18	(44.1) 90	
30≥	(47.1) 24	(39.7) 81	
Address			
Urban	(52.9) 27	(59.8) 122	0.413
rural	(47.1) 24	(40.2) 82	
Socio-economic level			
1	(23.5) 12	(30.9) 63	
2	(21.6) 11	(22.5) 46	0.744
3	(25.5) 13	(17.6) 36	
4	(11.8) 6	(12.5) 25	
5	(17.6) 9	34 (16.7) 34	
Diabetes			
Does not have	(82.4) 42	(78.9) 161	0.586
Has	(17.6) 9	(21.1) 43	
Marital status			
Single	(2) 1	(2) 4	
Married	(84.3) 43	(85.3) 174	0.495
Widow	(9.8) 5	(11.8) 24	
divorced	(3.9) 2	(1) 2	
Hormone Therapy			
positive	(2) 1	(2) 4	1
Negative	(98) 50	(98) 200	

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Table2. Breast cancer status of fertility factors in the case and control groups

Variable	Group	Number	Mean±SD	Confidence Range 95%	Minimum	Maximum	P-value
Age of first pregnancy	Case	49	22.76±4.99	21.32–24.19	14	37	0.005
	Control	193	20.8±4.16	20.21–21.39	14	38	
Menstrual age	Case	51	13.53±1.69	13.05–14	10	17	0.874
	Control	203	13.57±1.69	13.34–13.81	10	20	
The number of pregnancies	Case	50	3.76±2.22	3.13–4.39	0	13	0.032
	Control	200	4.67±2.76	4.29–5.05	0	14	
Age of first live birth	Case	49	23.57±4.94	22.15–24.99	15	38	0.006
	Control	193	21.66±4.07	21.08–22.24	14	38	
Number of children	Case	49	3.27±1.97	2.7–3.83	1	12	0.019
	Control	193	4.16±2.44	3.81–4.5	1	14	
Age of first abortion	Case	18	29±6.61	25.71–32.29	16	42	0.194
	Control	74	26.86±6.11	25.45–28.28	14	43	
Number of miscarriages	Case	49	0.45±0.68	0.25–0.64	0	3	0.354
	Control	193	0.58±0.89	0.45–0.7	0	4	
Lactation month	Case	49	16.71±7.41	14.58–18.84	0	24	0.451
	Control	193	17.58±7.09	16.57–18.58	0	48	
Age of hysterectomy	Case	8	46.75±6.79	41.08–52.43	35	57	0.589
	Control	36	44.83±9.39	41.65–48.01	29	64	
marriage age	Case	50	22.24±5.75	20.6–23.88	12	41	0.001
	Control	200	19.54±4.92	18.85–20.23	11	46	
Menopause Age	Case	39	46.77±5.89	44.86–48.68	30	58	0.343
	Control	134	47.82±6.13	46.77–48.78	29	61	

Table3. Results of single and multivariate logistic regression test for evaluation of fertility factors related to breast cancer

Variables	Univariate			Multivariate*		
	OR	CI 95%	P-value	OR	CI 95%	P-value
Age of first pregnancy ≤ (22)	2.09	1.09–4.00	0.026	2.76	1.12–6.79	0.027
Menstrual age (<13)	1.14	0.61–2.10	0.684	1.45	0.65–3.21	0.353
Parity (Noli Par)	0.72	0.15–3.34	0.671	**	**	**
Abortion History (No)	0.96	0.5–1.82	0.896	0.92	0.41–2.06	0.848
Breastfeeding (11 months)	1.37	0.6–3.15	0.452	1.47	0.50–4.26	0.476
Age of Menopause (46≤)	1.55	0.75–3.17	0.234	1.27	0.58–2.79	0.540

***Adjusting the effects of variables such as age of first pregnancy, age of menarche, number of pregnancies, history of abortion, duration of lactation, age of menopause, body mass index, educational level, socioeconomic status, area of residence, marital status, diabetes.**

**** Linear regression model for the Noli Par has not been answered due to the small sample size (n= 13).**

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Discussion

Single and multivariate logistic regression results for the studied factors showed that gestational age less than or equal to 22 years increases the odds of breast cancer by 2.76 times. According to the odds ratio observed, this factor is one of the major risk factors for high power in the region. In a study conducted by Sofi et al. in 2018 in Delhi, India, multiple regression results indicated that the odds of cancer in married people over 23 years were 2.4 times higher than in the control group (19) or in a study by Babita Et al., 2014 in India, 128 breast cancer patients were compared with 128 control groups for their fertility factors who were matched for age, with the age of first pregnancy that was significantly different between the two groups (20) which is similar to the results of the present study. The results of the present study and similar studies regarding pregnancy time as well as increasing prevalence of early pregnancy, which is about 11% in similar countries of Iran (21), should be used to increase public awareness and reduce the risk factor that this factor can be adjusted to make the necessary planning. Because pregnancy at the right age can even be a protective factor for breast cancer, as in a population-based case-control study of 20 breast cancer patients and 80 controls, the odds ratio of breast cancer in people with first gestational age under 30, was 0.3 times (22). Also in line with the results of the present study, other fertility factors had no association with breast cancer in our region. In a case-control study conducted by Giudici et al in Italy, 286 breast cancer patients and 578 people in control group which were age-matched with case group were evaluated for fertility factors. Fertility factors were not significantly different between the two groups, except lactation (23). In the present study, premenstrual menstruation, age of menopause, null parity, history of abortion and lactation were not significantly associated with breast cancer risk in our region. However, in a study by Khalis et al at a university hospital in Morocco, 237 cancer patients were compared with 237 age-matched controls in terms of fertility and menstrual factors. Logistic regression results showed that premenstrual and null parity increased the odds of breast cancer by 1.6 times and 3.77 times, respectively (24) or in a study by Balekouzou et al. in Central Africa, 174 breasts cancer patients were evaluated by 348 age-matched controls. The incidence of cancer in women with a history of miscarriage was 5.41 times, in nulliparous women was 1.98 times and in women with higher menstrual age was 0.18 times more than the control group (25). Also in a study by Tazhibi et al., 216 breast cancer patients and 41 healthy individuals were compared in terms of fertility and hormonal factors. Regression analysis results showed higher menopausal age is a risk factor (OR= 1.26) for breast cancer (26). This discrepancy between the present study and other studies may be due to differences in study design and control group selection or the matching of two groups based on OCP consumption as one of the main risk factors for breast cancer. One of the strengths of this study is that although it is a case-control study, it has been done on cohort entry phase data which has high validity in data collection and also the control group's selection from the normal population has been strength of the study. One of the limitations of the study was the sample size of the case group, which was selected four times to increase study capacity and overcome this shortcoming, this is one of the limitations of the case-control study, even the present study has a larger sample size than other population-based case studies in this field. The results of this study showed that gestational age is one of the major risk factors for breast cancer in the region that should be planned to increase public awareness and reduce this risk factor, which is a modifiable factor.

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