

## RESEARCH ARTICLE

# Risk of Breast Cancer in Relation to Reproductive Factors in North-west of Iran, 2013-2014

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## Abstract

More than one million new patients suffer from breast cancer annually in the world. In developed countries, breast cancer is the most common malignancy diagnosed among women, and in developing regions, it often ranks second to cervical cancer. This study aimed to investigate the relationship between incidence of breast cancer and reproductive factors in North-West of Iran. This retrospective analytical control-case study was conducted with 235 breast cancer patients and 235 women in the control group. Data collection tools included a set of questions with interviews and patient medical records. Data were analyzed using statistical tests: t-test, Chi-square, Fisher, and Pearson correlation coefficient. Significantly increased risks were associated between breast cancer and older age at first pregnancy, age at menopause and history of contraceptive use. A trend for decreasing risk were observed with increasing parity. Findings of this study showed no association between breast cancer and age at menarche. The study results suggested that physiological and reproductive factors may play important roles in the development breast cancer among Iranian women.

**Keywords:** Breast cancer - reproductive factors - oral contraceptive pills - Iran

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## Introduction

Breast cancer is the most common cancer among women in developed and developing countries (Ahmadian et al., 2012). In 2008, approximately 1.38 million new cases were diagnosed and approximately 458,000 deaths were recorded both in developed and developing countries (Iskandarsyah et al., 2014). The rates of breast cancer have increased over the past two decades (Asnarulkhadi et al., 2012). The WHO estimates that by the year 2020, the number of cases of cancer will double in developing countries (Seth et al., 2012). In Iran also, statistics indicate a huge increase in incidence of this disease Among Iranian women and It includes 22.9 percentage of invasive cancers in women and 16 percent of all cancers (Sabokbar et al., 2012). In developed countries, breast cancer is the most common malignancy diagnosed among women, and in developing regions, it ranks second to cervical cancer (Zeleniuchan et al., 2005). Among American women, breast cancer represents 32% of all new patients of cancer and is the second leading cause of cancer deaths (15%) after lung cancer (Hadjiiski et al., 2006). It is estimated that 211,240 patients suffer from invasive breast cancer in a year in the United States. These numbers represent a sharp increase over the past 30 years (Mousavi et al., 2006). Currently, in India, the incidence of breast cancer has steadily increased over the years and as many as 100,000 new patients are being detected every year. The

increase reported by the cancer registries is nearly 12% from 1985 to 2001, representing a 57% rise in India's cancer burden (Zeleniuch, 2005; Yip et al., 2006). Number of breast cancer cases is estimated to have reached 1.2 million worldwide. The incidence could go up by 50% i.e. 1.5 million by 2020 said world cancer report 2008. The report also points that breast cancer accounts for 16% of cancer deaths globally (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Statistics reveal a significant increase in this disease in the past 50 years, especially since 1970. This increase has even been seen in countries like India, Japan, and Korea, which used to have the lowest rates of breast cancer (Beiki et al., 2012). What causes breast cancer? And why a double and even triple increase is seen in recent decades? The Cancer Research Center consider reproductive factors such as age at menarche, age at menopause, parity, age at first delivery, and breast feeding influential (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). A study in Iran noted its risk factors as low number of childbirths, short breastfeeding period, family history, and use of contraceptives (Ghiasvand et al., 2011). A number of studies reported risk factors to include family history, early menarche, late menopause, and obesity at menopause (Collaborative Group on Hormonal Factors in Breast Cancer, 2009). Striking differences exist between countries in the incidence of breast cancer. The causes of these differences are unknown, but because incidence rates

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change in migrants, they are thought to be due to lifestyle rather than genetic differences (Tam et al., 2010). Use of oral contraceptive pills, as a potential risk factor, has long attracted interest of researchers. Contraceptive pills were globally marketed in 1960, and were made available in Iran in 1973. Some researchers are concerned that this disease increases with onset of contraceptive pill use, so that in the U.S., as in most places in the world, the increase in breast cancer has coincided with onset contraceptive pill use. The relationship between contraceptive pills and breast cancer incidence is controversial. A group of researchers concluded that use of contraceptive pills is related to and increases the incidence of breast cancer, and many reject such a relationship. The present study was conducted with the aim to determine the relationship between breast cancer and reproductive factors. The goal of this case control study was to examine breast cancer risk factors in populations with different risks for breast cancer. Since breast cancer is diagnosed in late stages in developing countries, these studies will help early prevention and timely diagnosis and treatment in high-risk people.

## Materials and Methods

This is an analytical case-control study, in which the effects of risk factors on incidence of breast cancer were investigated. There were 235 subjects in each of the case and control groups.

### Case group

Subjects in this group were selected by convenience sampling that attended chemotherapy and radiotherapy wards in Omid and Imam Khomainsi hospitals in Urmia on daily basis. Objectives of the study were explained to the subjects, and they were interviewed after obtaining their permission. Each interview lasted 20 minutes.

### Control group

Members for this group were selected through public call and from among samples attending women's clinics on daily basis. Breast examination was performed by a skillful physician. The subjects entered the study if healthy, and excluded if suspected, but were referred to relevant specialists for further examinations.

Necessary data were collected from both groups in relation to marital status, age, education, socio-economic status, history of breastfeeding, family history of cancer, history of benign mass, parity, age at menarche, regularity of menstrual cycle, use of contraceptive methods, history of diseases, history of alcohol use, history of hormone replacement therapy, history of infertility, duration of breastfeeding, use of cigarettes, history of chest radiography, and any contraindication for the pill, and then were matched with a higher number subjects in the control group. In this study, control and case groups were matched according to variables of age, socio-economic status, weight, and parity. Single women and those with history of chest radiography, family history of breast cancer, weighing over 80 kg, lack of breast feeding, history of female infertility hormone treatment, alcohol

and cigarette use were excluded from the study in both groups, and eventually, a number of women that did not match control group members were excluded. Data were analyzed with SPSS-18 using Fisher's exact test, Chi-square, student t-test, and Pearson Correlation Coefficient, and significant level was considered less than 0.05.

## Results

This study was conducted on case (235 women) and

**Table 1. Comparison Case and Controls by Selected Descriptive Characteristics**

Variable cancer	Case		Control		CI 95%
	Number	%	Number	%	
	235		235		
Age					
<40 years	56	23.9	48	20.4	p=0.163
40-49 years	81	34.5	110	46.8	
50-59 years	71	30.1	64	27.2	
≥60 years	27	11.5	13	5.6	
Mean	47.6		46.5		
Age at Marriage					
≤14 years	28	11.9	40	17	p=0.001
15-17 years	61	26	76	32.3	
18-20 years	62	26.3	70	29.8	
>20 years	84	35.8	49	20.9	
Occupation					
Worker	18	7.6	21	8.9	p=0.44
HOUSE Work	217	92.4	214	91.1	
Educational Level					
Illiterate	126	53.6	118	50.2	p=0.12
Primary	95	40.2	99	42.1	
Junior High	5	2.1	8	3	
Senior High	7	2.9	6	2.4	
College	2	0.8	4	1.7	

**Table 2. Risk of Breast Cancer According to the Female Reproductive Factors**

Variable cancer	Breast Cancer		p	
	Case 235	Control 235		
Age at menarche				
≤12	8 (3.4)	28 (12)	0.2 (0.11-0.52)	0.171
13	97 (41.3)	95 (40.4)	1.3 (0.71-1.49)	
14	78 (33.2)	74 (31.5)	1.1 (0.74-1.62)	
≥15 years	41 (17.1)	37 (15.7)	1.09(0.67-1.78)	
Don't know	11 (4.7)	1 (0.4)	-----	
Mean	14.9	13.78		
Age at menopause				
<50 years	91 (38.7)	66 (28.1)	0.6 (0.31-1.19)	0.02
50-59 years	32 (13.6)	15 (6.4)	1.5 (0.75-2.99)	
≥60 years	4 (2.7)	1 (0.4)	2.63(0.28-23.9)	
Premenopausal	108(46.0)	153(65.1)	0.6 (0.42-0.85)	
Mean	46.7	45.03		
Age at first pregnancy				
≤14	6 (2.6)	14 (6.0)	0.4 (0.15-1.09)	0.003
15-17	48 (20.2)	61 (26.0)	0.73(0.47-1.12)	
18-20	71 (29.8)	77 (33.1)	0.8 (0.6-1.31)	
>20	110(46.4)	83 (34.9)	1.63 (1.13-2.37)	
Mean	21.48	19.66		
Full term pregnancy				
1	19 (8.1)	6 (2.6)	2.78 (1.20-6.42)	0.022
2	59 (25.1)	48 (20.4)	1.34 (0.86-2.07)	
3	58 (25.3)	64 (27.2)	0.87 (0.57-1.32)	
≥4	99 (41.5)	117(49.8)	0.72 (0.50-1.03)	

**Table 3. Risk of Breast Cancer According to the Use of Combination Oral Contraceptives**

Group Pill users	Case		Control		OR		CI 95%	
	Number	Percent	Number	Percent				
OCP	165	70.2	124	52.8	2.11	1.44-3.08	p=0.001	
Others	63	26.8	92	39.1				
None	7	3	19	8.1				
	<12	29	6.17	12	6.9	60.2	1.31-3.01	p=0.219
	13-60	52	5.31	44	5.35	23.1	0.78-93.1	
	61-96	17	3.1	11	9.8	58.1	0.72-3.46	
	≥97	67	6.4	57	0.46	33.1	0.88-2.02	
Age at onset of using OCP								
	13-18	20	12.5	22	17.7	0.88	0.44-1.61	p=0.0001
	19-24	64	38.5	69	55.7	0.9	0.61-1.34	
	25-30	50	31.2	28	22.6	1.99	1.20-3.30	
	>30	29	17.8	5	4	6.47	2.46-17.04	
Age at discontinuing OCP								
	<25	20	12.1	25	20.2	0.78	0.42-1.44	p=0.004
	25-34	47	28.4	43	34.6	1.11	0.75-1.76	
	35-44	51	31	32	25.8	1.75	1.08-2.85	
	>45	24	14.5	8	6.5	3.22	1.41-7.34	
	Don't know	23	14	16	12.9	-		
Time since last use								
	12>	25	15.15	11	8.87	2.42	1.63-5.04	p=0.315
	12-36	17	10.31	7	5.65	2.54	1.03-6.24	
	37-96	37	22.42	25	20.16	1.65	0.91-2.70	
	>97	86	52.12	81	65.32	1.09	0.75-1.60	
	LD	116	70.3	106	85.4	1.18	0.82-1.70	p=0.002
	HD	49	29.7	20	14.6	2.83	1.62-4.93	
Used		165	2.7	124	8.52	11.2	1.44-3.08	p=0.001
Didn't use		70	8.29	111	2.47			

control (235 women) groups to investigate risk factors among women in West Azarbaijan Province. Results obtained showed that the majority of study subjects were aged 40 to 49 years, with the mean age in the case group 47.63 years and in control group 46.45 years. The two groups matched for age. Comparison of the two groups showed that the majority of study subjects were unemployed, illiterate, or with little literacy, with insignificant difference in terms of education level and employment status (socio-economic status). However, they were significantly different in terms of age at marriage ( $p=0.001$ ) (Table 1). Results also showed that age at menarche was 13-14 years in the majority of subjects in the case group (176 women, 74.9%) and in the control (169 women), 71.9%), and in this respect, the difference between the groups was insignificant ( $p=0.171$ ). The majority of subjects in the case group (108 patients, 46%) and in the control group (153 women, 65%) were premenopausal. Results showed that the two groups were different in terms of menopause age and odds of breast cancer increased with increasing menopause age. The majority of subjects (111 women (46.4%) in the case group, and 83 (34.9%) in the control) had their first pregnancy after the age of 20 years, and there was a significant difference between the two groups in terms of age at the first pregnancy ( $p=0.003$ ). History of the first pregnancy after age of 20 years increased risk of breast cancer (OR=1.63, CI 95%) (1.13-2.37). In terms of number of pregnancies: risk of cancer is reduced with increasing number of pregnancies, so that those with cancer had fewer pregnancies, with a significant difference between the two groups ( $p=0.02$ ). Odds ratio was 2.87

after the first pregnancy, 1.34 after the second, 0.87 after the third, and 0.72 after the fourth (Table 2). In terms of contraceptive use, 70.2% in the case group and 52.8% in the control used contraceptive pills. Chi-square test revealed a significant difference between the two groups ( $p=0.001$ ). In terms of duration of use, results showed mean duration of use was 94.5 month. in the case group, and 100.2 in the control, with an insignificant difference between two groups (Table 3). In terms of age at onset of use, there was a significant difference between use before and after 25 years of age, and in the case group, those that started taking pills at older age than 25 years, had higher odds ratio, compared to those that had their first use after age of 25 years. In relation to type of pill used, the difference between the two groups was significant, and among those with breast cancer, HD or a combination variety was used more (Table 3). In this study, there was an insignificant relationship between cervical cancer and factors such as age, discontinuation of pill use, and pattern of pill use (regular or alternate use).

## Discussion

In this study, mean age of those with breast cancer was 47.63 years. In a study by Shamsaldin, mean age was 49.1 years [19]. Mean age was 49.18 years in Najefzar study (Zare et al., 2013) and 51.3 years in Mosavi study (Mosavi et al., 2006) In this study, it was found that age at affliction in West Azarbaijan Province was lower than in other parts of Iran (Gao et al., 2000; Tamakoshi et al., 2005) consider early menarche and late menopause a risk factor, and also Bernstein et al, have concluded that risk

of breast cancer increases by 5% for every early menarche year and by 2.7% for every late menopause year (Bernstein et al., 2002; Tam et al., 2010). Results of an extensive study on 118964 women with breast cancer showed that early menarche and late menopause increased the risk [26]. In the present study, no relationship was found between age at menarche and incidence of breast cancer. Reliance on subjects' memory and passage of long time since menarche could have affected the above results. Also, there was a significant relationship between breast cancer and age at menopause, and with increasing menopause age to over 50 years, odds of cancer incidence reached 50.1, and more doubled in age over 60 years. A Chinese study showed that menopause after 50 years of age increased odds of breast cancer to 2.17, and menarche before 13 years of age increased the odds to 1.47 (Tam et al., 2010). Results of an extensive Japanese study on 38000 women showed no relationship between breast cancer and age at menarche or menopause (Tamakoshi et al., 2005). In Iran, menopause age may be lower than in some parts of the world. Also, mean age at diagnosis in this study was lower than in others, which could affect the results. Mean age at the first pregnancy in studies by Indian researchers was 21.6 years ( Pakseresht et al., 2009) and in the present study, mean age at the first pregnancy was 21.48 in the case group and 19.66 in the control group. In terms of age at first pregnancy, there was a significant difference between case and control group subjects, and those over 20 years of age had higher odds than control group, OR=1.63 with 95% confidence interval (1.13-2.37). Some studies consider increased number of pregnancies as a protective factor against breast cancer. A Danish study indicated that more pregnancies reduce the risk of affliction (Ewertz et al., 1988). The present study showed OR=2.78 for the first pregnancy, which reduced to OR=0.72 after 4 pregnancies. Kelsey considers nulliparity after 40 years old dangerous (Kelsey et al., 1993). While, in the above study, it increased the odds in lower ages as well.

In relation to contraceptive types, contraceptive pills had the highest frequency in both case and control groups (70.2% in case group, and 52.8% in control). In studies by Vessy et al. (1996) and Brinton et al. and Negrini et al. (1990), pills had the highest use compared to other contraceptive methods. In terms of history of use, the comparison showed a significant difference between the two groups. Wang et al. (1992) Stanford et al. (1995), Fasal et al. (1975) and Kumle et al. (2002) also found a relationship between history of use of pills and breast cancer. While in a study by Tavani on 373 patients and control group, under 40 years, no relationship was found between use of the pill and incidence of cancer (Tavani et al., 1993). Whiteman et al. (2007) not only did not find use of the pill a risk factor, but also considered it a protective factor. In this study, age groups had not been separated. Generally, in this study use of contraceptive pills doubled odds of breast cancer {OR=2.11, with 95% confidence interval (1.44-3.08)}. Odds ratio was 2.2 in a study conducted in Isfahan Province (Ehsanpour et al., 2013) 2.38 in a study by Shobiri et al. (2010), and 3.02 in Paul's study. (Lodha et al., 2011).

In conclusion, results of this study showed that, in

Iran, age at being diagnosed with breast cancer is lower than in many parts of the world, and that incidence of breast cancer is associated with high age at the first pregnancy, high menopause age, nulliparity, and use of contraceptive pills, which double the incidence of breast cancer. Therefore, in Iran, screening for breast cancer in high-risk people is highly necessary.

Results of this study indicate that high risk women need more preventive actions and screening.

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