RESEARCH COMMUNICATION

Reproductive Characteristics and the Risk of Breast Cancer - A Case-control Study in Iran

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Abstract

Breast cancer is a common malignancy for women in most parts of the world and the incidence in Iranian women is growing. The patients are relatively younger than their western counterparts. The present hospital based case-control study was designed to determine roles of reproductive factors for breast cancer among women in Iran. Conducted at a teaching hospital in Tehran, Iranin 2004, the study covered a total of 303 cases of breast cancer and 303 healthy controls. Cases were identified through the Oncology Department of a university hospital and controls were collected from other wards or out-patient clinics at the same hospital. Control subjects were matched to patients for age. Informed consent was obtained from all cases and controls then demographic and reproductive factors were ascertained by in-person interview using a constructed questionnaire. Odds ratios and their 95% confidence intervals for breast cancer were derived using logistic regression analysis. The mean ±SD ages of cases and controls were 48.8 ± 9.8 and 50.2 ± 11.1 years, respectively, (range 24-84). The final model for multiple analysis indicated that never married, post menopause, age at first live birth, number of live births, use of oral contraceptive pills, and history of chest X-rays between adolescence and 30 yrs of age, were significantly associated with breast cancer. Variables such as higher education, early age at menarche, abortion, breast feeding and its duration were not significant risk factors .

Key Words: Breast cancer - case-control study - reproductive factors - Iranian women.

Asian Pacific J Cancer Prev, **6**, 370-375

Introduction

Breast cancer is the most common type of cancer among women in the world (Humpel et al., 2004), the incidence rising rapidly from the 1970s to the 1990s in most countries (Dalthius et al., 2005). In 2000, more than one million women were diagnosed (22% of all female cancers) and 373, 000 women died (14% of all cancer deaths among women) of breast cancer (Parkin et al. 2001). Breast cancer incidence and mortality rates vary greatly with the geographic location, with global differences in incidence rates and fluctuation in rates within a country affected by changes in risk factor prevalence and secular trends in breast cancer diagnosis. Adaptation of a western lifestyle has been postulated as being one of the primary reasons for increasing breast cancer rates in developing countries and among Asian and Asian American women (Ziegler et al 1993, Stanford et al 1995).

In Iran, breast cancer constitutes 21.4 % of all cancer cases reported in the country. The crude incidence rate of breast cancer in women is 22.4 per 100000 populations (Shamsa et al., 2002). Data indicated that breast cancer has increased in Iran and since 1999 its incidence has ranked highest in the Iranian cancer registry data (Shamsa et al., 2002). The age-specific incidence distributions of breast cancer in Iran and western women are different (Harirchi et al., 2000). The literature indicates that the mean age of breast cancer patients is over 55 years in the Western world (Miller et al., 1993), while Iranian breast cancer patients are about 10 years younger(Harirchi et al., 2000).

The objective of this study was to ascertain the role of reproductive risk factors (parity, breastfeeding, abortion, age at menarche) for breast cancer in Iran and to identify groups at a high risk of breast cancer occurrence using case-control groups.

Materials and Methods

A hospital based case-control study was carried out to elucidate roles of reproductive factors in breast cancer. The total sample comprised of 303 breast cancer patients and

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303 hospital controls. All the cases and controls were selected from a teaching university hospital in North Tehran.

The inclusion criteria for the hospital-case group were female patients having histopathologically confirmed breast cancer. They were identified through Oncology and Surgery department. Hospital controls were selected as patients without current or past history of breast cancer and collected from other wards or out-patientsû clinics at the same hospital. Control subjects were matched to cases on age (_2 years). Data were collected through interview using structured questionnaires comprising several parts: Demographic variables such as age, place of residence in the past 20 years, educational level, marital status, past history of breast diseases and family history of breast cancer. Reproductive variables were included age at first menarche, history of menstruation, pregnancies, age at first full-term pregnancy and live birth, number of live birth and abortions, breastfeeding and its duration, use of oral contraceptives and menopause.

Women were classified as menopause if they had not menstruated during 1 year before the date of interview. A full-term pregnancy was defined as pregnancy lasting 8 months or longer. The variables were measured for cases up to date of breast cancer diagnosis and for controls up to the date of interview. Other risk factors such as, complete smoking history, were measured, and obesity was determined by body mass index (BMI) and waist to hip ratio (WHR).

Verbal consent was obtained from all subjects, and study procedures were approved by the research committee of the University. Approval was obtained also from the director of hospital.

The data were analyzed using univariate and multiple logistic regression models. Associated risks were calculated using Odds Ratio (OR) and its 95% confidence interval. We constructed stepwise logistic regression analysis employing the significant and borderline variables selected through univariate analysis.

Results

Mean ±SD age of cases and controls was 48.7 ± 9.8 and 50.2± 11.1 years, respectively with median of 48 years (range 24-84 years).

Table1 shows the main risk factors for breast cancer, among Iranian Women, in a univariete logistic regression analysis. In this hospital case-control model, the risk for women with at least a college education was 4.81 fold that for those with no or less education (95% CI= 2.36-9.79). Compared to ever married women, the risk for never married women for breast cancer was 8.48 fold (95% CI= 1.94-37.10). Women with lower age at menarche (12 and below) were at slightly higher risk of breast cancer than those with older age at first menarch (15 and above), but the difference between these two groups was not statistically significant. Women who were menopause had a higher risk of breast cancer (OR 2.97, 95% CI= 2.09-4.20). Nuliparous women were at slightly higher risk of breast cancer than parous women but the difference was not significanct. Variables such as number of pregnancy and number of live birth were significantly different between case and control groups.

Table1. Demographics and Reproductive Characteristics of Cases and Controls, Their Associated Odds Ratio and its 95% Confidence Intervals for Breast Cancer

P Value	OR(95% CI)	Controls	Cases	Characteristics
P<0.001				Education level
	1.0 (reference)	183 (61.2)	155 (51.1)	Primary or lower
	1.5 (0.91-2.96)	46 (15.4)	42 (13.9)	Middle school
	2.0 (1.27-3.3)	57 (19.0)	69 (22.8)	High school
	4.81 (2.36-9.79)	13 (4.4)	37 (12.2)	College and university
P<0.005				Marital status
	1.0 (reference)	301 (99.3)	286 (94.7)	ever married
	8.48 (1.94-37.10)	2 (0.7)	16 (5.3)	never married
NS				Age at first Menstruation
	1.32 (0.82-2.10)	58 (19.3)	69 (23.1)	<=12
	1.08 (0.69-1.67)	80 (26.6)	78 (26.2)	13
	1.05(0.67-1.63)	79 (26.2)	75 (25.2)	14
	1.0 (reference)	84 (27.9)	76 (25.5)	>=15
NS				Total Menstrual duration
	2.1 (0.97-4.56)	11 (7.4)	28 (14.1)	<=24
	0.75 (0.41-1.37)	32 (21.5)	29 (14.6)	25-29
	1.24 (.075-2.06)	44 (29.5)	66 (33.3)	30-34
	1.0 (reference)	62 (41.6)	75 (37.9)	>=35
P<0.001				Menopause status
	2.97 (2.09-4.20)	161 (53.1)	234 (77.2)	Post menopause
	1.0 (reference)	142 (46.9)	69 (22.8)	Premenopause
NS				Parity
	1.0 (reference)	291 (96.0)	280 (92.7)	Parous
	1.92 (0.93-3.96)	12 (4.0)	22 (7.3)	Nuliparous

Table 1 (continued)

P Value	OR(95% CI)	Controls	Cases	Characteristics
P<0.004				No of pregnancy
	2.95 (1.34-6.46)	12 (4.0)	22 (7.3)	0
	1.52 (0.91-2.55)	55 (18.2)	52 (17.2)	1-2
	2.16 (1.38-3.39)	84 (27.7)	113 (37.4)	3-4
	1.41 (0.87-2.29)	73 (24.1)	64 (21.1)	5-6
	1.0(reference)	79 (26.1)	51 (16.9)	>=7
P<0.01				No of live birth
	3.93 (1.71-9.05)	12 (4.0)	22 (7.3)	0
	2.28 (1.32-3.93)	78 (25.7)	83 (27.50)	1-2
	2.64 (1.56-4.46)	94 (31.0)	116 (38.4)	3-4
	1.83 (1.03-3.27)	62 (20.5)	53 (17.5)	5-6
	1.0 (reference)	57 (18.8)	28 (9.3)	>=7
P<0.0001				Age at first live birth (yrs)
	1.0 (reference)	171 (59.6)	111 (40.4)	<20
	2.23 (1.53-3.25)	78 (27.2)	113 (41.1)	20-24
	1.54 (0.89-2.68)	31 (10.8)	31 (11.3)	25-29
	4.39 (1.80-10.73)	7 (2.4)	20 (7.3)	>=30
P<0.001				History of abortion
	0.44 (0.31- 0.63)	121 (41.2)	66 (23.6)	Yes
	1.0 (reference)	173 (58.8)	214 (76.4)	No
P<0.03				Breastfeeding history
	1.0 (reference)	281 (92.7)	265 (87.5)	Yes
	1.84 (1.06-3.19)	22 (7.3)	38 (12.5)	No
P<0.001				Total Breast feeding (months)
	2.35 (1.33-4.16)	22 (7.3)	40 (13.2)	0
	1.33 (0.79-2.23)	35 (11.6)	36 (11.9)	1-12
	0.90 (0.52-1.54)	39 (12.9)	27 (8.9)	13-24
	2.09 (1.34-3.25)	44 (14.5)	71 (23.4)	25-48
	1.0 (reference)	163 (53.8)	129 (42.6)	>48
P<0.006				Family history of breast cancer
	2.09 (1.22-3.55)	23 (7.6)	44 (14.7)	Yes
	1.0 (reference)	279 (92.4)	256 (85.3)	No
NS				No of breast cancer in relatives
	1.0 (reference)	281 (92.7)	265 (87.5)	0
	1.41 (0.76-2.63)	19 (6.3)	25 (8.3)	1
	4.66 (1.33-16.53)	3 (1.0)	13 (4.7)	2-5
P<0.013				Chest X-Ray between adolescence and age of 30 yrs
	1.59 (1.10-2.29)	67 (22.2)	92 (31.2)	Yes
	1.0 (reference)	235 (77.8)	203 (68.8)	No
P<0.02				Oral Contraceptive Use
	1.50 (1.09-2.07)	149 (49.2)	177 (59)	Yes
	1.0 (reference)	154 (50.8)	123 (41)	No
NS				History of breast disease
	1.03 (0.55-1.89)	22 (7.3)	22 (7.4)	Yes
	1.0 (reference)	281 (92.7)	274 (92.6)	No

CI: Confidence Interval, OR: Odds Ratio

According to table 1, the higher the number of live birth, the lower the risk for developing breast cancer (p<0.01): the risk of women who had given 1-2, 3-4, 5-6 and 7 or more birth, were, respectively, 3.93 fold (95% CI: 1.71-9.05), 2.28 fold (95% CI: 1.32-3.93), 2.64 fold (95% CI: 1.56-4.46), and 1.83 fold (95% CI: 1.03-3.27) that for women who had given no live birth. Women who were older at the first live birth pregnancy had a higher risk of breast cancer (P< 0.01).

Compared to women without the experience of abortion, the risk for women who had aborted was lower as the risk for reference group (OR 0.44 95% CI= 0.31-0.63). Women with no experience of breast feeding were at higher risk of breast cancer than those who had breast fed (OR 1.84, 95% CI= 1.06-3.19). In comparison with women without the experience of breast feeding, the risk for women who had breastfed for up to 12months was lower as the risk in the reference group (OR= 1.33 95% CI= 0.79-2.23) , whereas in those who had breastfed for 13 to 24 months and for more than 24 months the risks were 0.90 fold (95% CI= 0.52-1.54) and 2.09 fold (95% CI= 1.34-3.25) that in the reference group, respectively. These data indicate that the risk of breast

Table 2. ORs and 95% CIs of major risk factors associated with breast cancer, result of a multiple logistic regression analysis.

P-value	OR(95% CI)	Characteristics
		Age at first live birth
	1.0 (reference)	<20
0.008	1.82 (1.17-2.84)	20-24
0.715	1.14 (0.56-2.32)	25-29
0.03	3.46 (1.13-10.60)	>=30
0.931	1.06 (0.28-4.05)	Nulliparous
		No of live birth
0.377	2.22 (0.38-13.03)	0
0.009	2.58 (1.27-5.25)	1-2
0.004	2.43 (1.32-4.49)	3-4
0.115	1.68 (0.88-3.21)	5-6
	1.0 (reference)	>=7
		Chest X-Ray between adolescence and age of 30
0.02	1.67 (1.08-2.58)	Yes
	1.0 (reference)	No
		Oral Contraceptive Use
0.001	1.95 (1.32-2.87)	Yes
	1.0 (reference)	No
		Menopause status
P<0.001	3.59 (2.36-5.47)	Post menopause
	1.0 (reference)	Premenouse
		Marital status
0.017	9.82 (1.50-64.16)	Never married
	1.0 (reference)	Ever married

cancer significantly increases as breast feeding duration decreases (p< .001).

The risk of breast cancer for women with a family history of breast cancer was 2.09 fold that for women without any family history (95% CI=1.22 ñ 3.55). For those who had breast cancer in relatives for 1 breast cancer in family and for 2-5 breast cancer in relatives the risks were 1.41 fold (95% CI= 0.76-2.63) and 4.66 fold (95% CI=1 .33-16.53) that in reference group, respectively.

The risk for breast cancer for women with a history of chest X-ray during adolescence and 30 years old was 1.59 that for women without an X-Ray history (95% CI= 1.10-2.29). The odds ratio for developing breast cancer for those ever using oral contraceptive was 1.5 (95% CI= 1.09-2.07). Variable such as the previous history of breast lesion or benign tumors was not significant risk factors for breast cancer.

Table2 shows ORs and 95% CIs of breast cancer associated with major risk factors for cases and controls in multiple logistic regression analysis. The final model on multivariate analysis indicated that marital status, never married : OR 9.82, (95% CI 1.50-64.16), menopause: OR 3.59 (95% CI 2.36-5.46), No. of live birth for none, 1-2, 3-4, 5-,6 the ORs are 2.22 (95% CI 0.38-13.03), 2/58 (95% CI 1.27-5.25),, 2.43 (95% CI 1.32-4.49), and 1.68 95% CI 0.88-3.22), respectively and for age at first live birth for 20-24,25-29,>=30, and nuliparous is 1.82 (95% CI 1.17-2.84), 1.14 (95% CI 0.562-2.32), 3.46 (95% CI 1.13-10.60), 1.06 (95% CI 0.29-4.05), use of oral contraceptive pills: OR 1.95 (95% CI 1.32-2.87), and history of chest X-Ray between adolescence to 30 yrs: OR 1.67 ,(95% CI 1.08-2.58), were significantly associated with breast cancer. Variables such as higher education, early age at menarche, family history, abortion, breast feeding and duration of breast feeding were not significant risk factors for breast cancer.

Discussion

In this hospital based case-control study, marital status (never married), menopausal status, lower number of live births, age at first live birth (an older age at the first full-term pregnancy) and oral contraceptive use, chest X-ray exposure between adolescence to 30 years were recognized as the main risk factors for breast cancer among Iranian women. The findings in this study show that never married women were at high risk for breast cancer, and marital status was found to be the strongest protective factor in this study. This finding is similar to that from previous case-control study (Ebrahimi et al., 2002,). Whereas it was reported as a weak protective factor in studies on Western women (Kelsey et al. 1993). It seems that marital status by itself is not a determinant factor for the risk of breast cancer, and the main protective effect is from the age at first full term pregnancy. In this study on multivariate analysis, no association was found with parity and Breast Cancer but an association was found with age at first live birth and number of live birth. Evidenced suggests that there is an interaction between marital status and parity (McCredie et al. 1998). There is evidence to show that a significant positive interaction of genetic susceptibility and number of full term pregnancies and a reduced protective effects of a higher number of full-term pregnancies and a high parity among genetically susceptible women (Becher et al. 2003). Several authors have considered a possible interaction between a family history of breast cancer and parity and observed a lack of protection from multiple births in women with a family history of breast cancer (Negri et al. 1988; Colditz et al. 1996). Also there is evidence suggesting that the more full term pregnancies a women has had , the lower her risk of breast cancer diagnosed after about 45 years of age, but that a higher number of full term pregnancies may increase the risk of breast cancer at earlier ages. In addition, evidence is that an older age at any delivery may confer an increased risk (Kelsey et al., 1993).

In our study abortion do not affect a women's risk of having breast cancer (data on abortion obtained from interviews rather than the population registries). Evidence indicating a positive interaction of abortion and a history of abortion is associated with higher breast cancer in genetically susceptible women (Becher et al. 2003). In another study (Tang et al., 2000), the risk of breast cancer was not found to be associated with a prior induced abortion, if followed at some later time by pregnancy and childbirth.

Later age at menarche was shown to be protective in women with a positive family history. Evidence indicating a stronger protective effect of later age at menarche for

women with genetic susceptibility (Becher et al. 2003). In our study we did not found any significant association between age at menarche and high risk of Breast Cancer.

Becher (Becher et al. 2003) did not observe an effect of age at first birth on breast cancer risk. Gail and Greene (Gail et al. 1989), noted that a negative interaction was observed between age at first live birth and number of affected first degree relatives. This interaction was found by Bondy (Bondy et al. 1994).

Although childbearing is acknowledged as protective against breast cancer, the role of breast feeding remains uncertain. In our study, breastfeeding was found to carry a significant association with breast caner in the initial analysis, but the final model indicates no association between breastfeeding and Breast Cancer. Child bearing is known to be protective factors against breast cancer; however, the contribution that breast feeding makes to this protective effect is debated (Breast cancer and breastfeeding, Collaborating group on hormonal factors in breast cancer. 2002). In one study, the investigators who were combining data from seven countries in the international collaborative case control study, found no overall relation between breastfeeding and breast cancer. This finding led to the belief that any such apparent relationship was spurious and due to the confounding effects of parity (Michel et al., 1996). There are evidenced that relative risk of breast cancer decreased with increasing parity in both women who had and those who had not breast fed an infant. The Relative Risk (RR) of breast cancer declined 4.3% for every 12 months of breastfeeding and 7% for each birth. This association was found in both developed and developing countries and was unaffected by age, ethnic origin, number of births, age at birth of the first child, and menopausal status (Breast cancer and breastfeeding, Collaborating group on hormonal factors in breast cancer. 2002). Bacher found high parity and longer duration of breast feeding reduced Breast Cancer risk significantly, a history of abortion increased risk and age at menarche showed no significant effect. They found women the most likely to have a genetic susceptibility, high parity was less protective. No evidence for genetic-environment interaction was found for breast feeding and abortion.

In our study menopause affect a women's risk of having breast cancer. Talamini and Hsieh observe an effect of history of menopause on high risk of breast cancer (Talamini et al. 1996, Hsieh et al. 1990).

Evidence for the effect of oral contraceptive use on the risk of breast cancer is conflicting (Rookus et al., 1994). There are evidenced suggested that there was no significant difference between users and nonusers of oral contraceptive and increase the risk of developing breast cancer among women (Marchbanks et al., 2002), (Tomasson et al., 1996), (Tessaro et al., 2001). There are evidenced suggested the relation of OC use and developing breast cancer (Hankinson et al., 1997). In present case-control based interview study of women, use of oral contraceptive (OC) seems to increase slightly the risk of developing breast cancer among women in Iran. The increased odds ratio among those used OC for unknown periods of time may be related to recall bias, i.e. the possibility that women diagnosed with breast cancer either remember better or are forced to recall the OC use more effectively than others. These results donût give any reason to recommended changes in the current use of oral contraceptives. However, it has not been possible to consider various estrogen / progesterone combinations which may be necessary in order to come to a more definite conclusion. Considering the benefit of OC, however, there is a need for more studies of OC use in well defined groups in order to come to a decision on whether the use of OC increases the risk of breast cancer in these special groups or not.

Our study showed that X-ray exposure between adolescence to 30 years old was recognized as the main risk factor for breast cancer. Evidence indicating that the risk of breast cancer among X-ray worker enhanced significantly than the control group and it occurred more in those who engaged in X-ray work more than 25 years and those who are exposed before age 30 (Wang et al. 1996) . Wang found significant risk factors are accumulative radiation dose of breast, obesity and family history of breast cancer. In addition, interaction could exist between obesity, non-lactation history and occupational X-ray exposure.

In conclusion, the lack of significant association of some variables such as family history and the risk of developing breast cancer in final model may be related to power of study to estimate the risk. Also we should be aware of the limitation of the case control study, including case and control ascertainment and representation.

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