

Breast Feeding and Breast Cancer Risk: A Case-control Study in Korea

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ABSTRACT

We carried out a case-control study to investigate protective effect of lactating against breast cancer in Korea. Cases ($n = 108$) were the newly histologically identified breast cancer between December 1997 and August 1999. Hospital-based controls were selected by frequency matching method with age (± 4 age) and menopausal status from the patients at the same hospital in the plastic surgery, general surgery and ophthalmology department. Interviews included information on general characteristics of subjects, disease history, family history of breast cancer, vitamin supplementation, alcohol intake, food intake, and reproductive factors as well as lactation history. Odds ratio (OR) and 95% Confidence Intervals (CI) were calculated by using unconditional logistic regression. Age distribution of case and control subjects were similar. Late menarche age ≥ 17 in premenopausal women was related to the lower risk of breast cancer OR = 0.41, 95% CI = 0.28-0.91. Family history of breast cancer was related to the higher risk of breast cancer only in premenopausal women (OR = 2.07, 95% CI = 1.35-2.71). Higher body mass index (> 30) were associated with higher risk of breast cancer in postmenopausal women. For premenopausal women, women who had lactated ≥ 12 months to the first child had a significantly lower risk (OR = 0.53, 95% CI = 0.24-0.97) than the women had no breast feeding experience. However, results from postmenopausal women did not show an association with decreased breast cancer risk. These findings suggest that lactation may be a protective factor of breast cancer in Korean women.

KEY WORDS: breast cancer, case-control study, menopausal status, breast feeding.

INTRODUCTION

Breast cancer has been increased over the past 10 years in Korea.¹⁾ Studies searching for the risk factors of breast cancer have focused on the preventable factors and most researchers have been interested in lifetime lactation. The hypothesis that breast feeding may prevent breast cancer was raised as early as the 1920s.²⁾ It has turned out that lifetime lactation in relation to breast cancer risk differ as to menopausal status and specially there are some indications that lactation may be protective only for premenopausal breast cancer. A number of epidemiological studies have reported a reduced risk of breast cancer among women who lactated,³⁻⁴⁾ but they are still controversial. Two international studies found no or only weak association,⁵⁻⁶⁾ and there are some reports that breast feeding may be protective only for premenopausal breast cancer.⁷⁻⁸⁾ Several mechanisms have been proposed through biological studies. Lactation suppresses ovulation, and there may be a direct relation between the number of ovulatory cycles in lifetime of women and breast cancer risk. There is one re-

port that lactation may confer some terminal differentiation of ductal epithelial cell that render them less susceptible to carcinogenic agents.⁹⁾ In one study, lactating women had lower levels of estrogen than non-lactating women and this reduction persisted after lactation had ceased.¹⁰⁾ There are reports that age at first lactation may be important,¹¹⁾ and that duration of lactation is of importance.¹²⁻¹⁴⁾ The role of breast feeding in the prevention of breast cancer is of interest because it is a modifiable risk factor, and it could contribute to decreasing incidence of breast cancer. With the use of data from a hospital-based case-control study of breast cancer, we investigated the association of breast cancer and breast feeding in Korean women.

SUBJECTS AND METHODS

1. Ascertainment of study subjects

Women whose histologically confirmed first diagnosis of breast cancer between December 1997 and August 1999 at Hanyang and Soonchunhyang University Hospital in Seoul, Korea were eligible for selection as cases. Their ages were restricted to between 20 and 69. Hospital-based controls were women, who were selected by freque-

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ncy matching from patients at the same hospital in the departments of plastic surgery, general surgery and ophthalmology. Controls were women who had no past history of breast cancer, other cancer history, and no history of disease like diabetes and hypertension. Matching variables were age (± 4 age) and menopausal status. There were 138 eligible cases, four of whom refused, and 11 whose cancer was benign. Because of subjects who were aged > 70 years ($n = 5$) were interviewed by surrogate subjects and 8 subjects did not match menopausal status, they were excluded in analyses. The remaining 108 cases were enrolled. Among 149 controls, those who have had diabetes or hypertension were excluded and the final number of controls was 121.

2. Data collection

The data were collected from 1997 to 1999 in Seoul, Korea. Study subjects were interviewed by trained interviewers and socioeconomic status and medical information was collected from the study subjects by use of interviewer-administered questionnaire. Information on oth-

er breast cancer risk factors, including age, height, weight, number of years of education, medical history, reproductive history, and hormone therapy was obtained from each subject by individual interview. As part of the breast feeding history, subjects were asked whether they had lactated for each of their children and if so, what was the total duration of breast feeding and months of breast feeding of the first child.

3. Statistical analysis

In order to assess the role of lactation on breast cancer risk, lactation analyses were limited to women who only had been pregnant. Odds ratio (OR) and 95% Confidence Intervals (CI) were calculated by using unconditional logistic regression. Adjusted analyses included control for age, age at menarche, and family history of breast cancer in premenopausal women, and, for postmenopausal women, age, and Body Mass Index. To define difference according to the menopausal status, all analyses were stratified on menopausal status.

Table 1. General characteristics of cases and controls, Seoul, Korea, 1997 – 1999

Variables	Premenopausal		Postmenopausal ¹⁾		All Women	
	Case	Control	Case	Control	Case	Control
Sex						
Female	60 (100) ²⁾	67 (100)	48 (100)	54 (100)	108 (100)	121 (100)
Age (year)						
20 – 29	7 (11.6)	8 (11.9)	–	–	7 (6.5)	8 (6.6)
30 – 39	18 (30.0)	21 (31.3)	–	–	18 (16.5)	21 (17.4)
40 – 49	33 (55.0)	37 (55.2)	3 (6.3)	6 (11.1)	36 (33.3)	43 (35.5)
50 – 59	2 (2.9)	1 (1.6)	33 (68.8)	35 (64.8)	35 (32.4)	36 (29.8)
60 – 69	–	–	12 (24.9)	13 (24.1)	12 (11.1)	13 (10.7)
Marital status						
Married	45 (75.0)	54 (80.6)	39 (81.3)	45 (83.3)	84 (77.8)	99 (81.8)
Unmarried	14 (23.3)	8 (11.9)	2 (4.2)	1 (1.9)	16 (14.9)	9 (7.4)
Widowed	1 (1.7)	5 (7.5)	7 (14.6)	8 (14.8)	8 (7.3)	13 (10.7)
Occupation						
Unemployed	2 (2.9)	1 (1.6)	–	–	2 (1.9)	1 (0.8)
Housewife	45 (75.0)	48 (7.5)	36 (75.0)	40 (74.1)	81 (75.0)	88 (72.7)
Farmer	2 (2.9)	3 (4.5)	2 (4.2)	1 (1.9)	4 (3.7)	4 (3.3)
Professional	7 (11.6)	10 (14.9)	5 (10.4)	8 (14.8)	12 (11.1)	18 (17.4)
Sales/Service	4 (7.6)	5 (7.5)	5 (10.4)	5 (9.2)	10 (9.3)	10 (8.3)
Family history of breast cancer						
None	53 (88.3)	63 (94.0)	45 (93.6)	52 (96.3)	98 (90.7)	115 (95.0)
Yes	7 (11.7)	4 (6.0)	3 (6.4)	2 (3.7)	10 (9.3)	6 (5.0)
Body mass index (BMI)						
< 20	11 (18.3)	9 (13.6)	5 (10.4)	6 (11.2)	16 (14.8)	15 (12.4)
20.00 – 24.99	20 (33.4)	28 (41.8)	11 (22.9)	14 (25.9)	31 (28.7)	42 (34.7)
25.00 – 29.99	18 (30.0)	18 (26.7)	17 (35.4)	22 (40.7)	35 (32.4)	40 (33.0)
≥ 30	11 (18.3)	12 (17.9)	15 (31.3)	12 (22.2)	26 (24.0)	24 (19.9)

1): This category included only natural menopause women 2): No. (%)

RESULTS

1. General characteristics of subjects and other variables and breast cancer risk

Characteristics of the cases and controls included in this study are shown in Table 1.

Cases and controls were similar to the distribution in ages and among of cases, premenopausal women made up 55.6%, and postmenopausal women accounted for 44.4%. Among all subjects, there was a high incidence of breast cancer among women in their 40s and 50s. Also, the distribution of marital status, occupation, and body mass index was similar for cases and controls.

Odds ratios and 95% confidence intervals of reproductive factors recognized as potential confounders on the association between breast feeding and breast cancer are presented in Table 2. Age at menarche for ≥ 17 in premenopausal women was significantly related to the lower risk of breast cancer (OR = 0.41, 95% CI = 0.28 - 0.91). However, the odds ratio associated with total menstrual period, pregnancy, and total number of full term deliv-

Table 2. Odds ratio (OR) of breast cancer in relation to reproductive factors

Variable	Premenopausal women			Postmenopausal women ¹⁾		
	Case No.	Control No.	OR ²⁾	Case No.	Control No.	OR ³⁾
Age at menarche						
≤ 13	8	5	1.00	5	5	1.00
14 - 16	41	49	0.63 (0.35 - 1.08) ⁵⁾	31	41	0.82 (0.84 - 2.11)
≥ 17	11	13	0.41 (0.28 - 0.91)*	12	8	1.32 (0.96 - 3.14)
Total menstrual period (Year)						
< 25	-	-	-	5	7	1.00
25 - 35	-	-	-	30	36	1.12 (0.67 - 2.43)
> 35	-	-	-	13	11	1.61 (0.87 - 2.14)
Pregnancy						
Never	16	11	1.00	4	3	1.00
Ever	44	56	0.63 (0.35 - 1.58)	44	51	0.82 (0.84 - 3.11)
Total No. of full term delivery ⁴⁾						
None	18	12	1.00	5	6	1.00
1 - 3	28	32	0.68 (0.76 - 2.47)	16	18	1.02 (0.36 - 1.43)
> 3	14	23	0.54 (0.39 - 1.79)	27	30	1.01 (0.87 - 3.14)

1): This category included only natural menopausal women

2): Odds ratio in premenopausal women adjusted for age

3): Odds ratio in postmenopausal women adjusted for age

4): Only among women ever pregnant

5): 95% Confidence Interval (CI) * : $p < 0.05$

ries did not show any significant difference between premenopausal women and postmenopausal women. Table 3 shows the odds ratio (OR) of breast cancer in relation to family history of breast cancer and past history of benign breast disease. Family history of breast cancer was related to the higher risk of breast cancer only in premenopausal women (OR = 2.07, 95% CI = 1.35 - 2.71). Past history of benign breast cancer was not associated with the risk of breast cancer in this study. Risk associated with height, and current body mass index (BMI) is shown in Table 4. The association between body mass index and breast cancer was clearly different according to menopausal status in this study. Higher body mass index (> 30) was associated with higher risk of postmenopausal breast cancer. Women who had a body mass index over 30 had a 98%

Table 3. Odds ratio (OR) of breast cancer in relation to family history of breast cancer and past history of benign breast disease

Variable	Premenopausal women			Postmenopausal women ¹⁾		
	Case No.	Control No.	OR ²⁾	Case No.	Control No.	OR ³⁾
Family history of breast cancer						
No	53	63	1.00	45	52	1.00
Yes	7	4	2.07 (1.35 - 2.71) ⁴⁾ *	3	2	1.62 (0.84 - 2.11)
Past history of benign breast cancer						
No	51	60	1.00	43	50	1.00
Yes	9	7	1.61 (0.76 - 2.17)	5	4	0.91 (0.87 - 1.84)

1): This category included only natural menopause women

2): Odds ratio in premenopausal women adjusted for age

3): Odds ratio in postmenopausal women adjusted for age

4): 95% Confidence interval (CI) * $p < 0.05$

Table 4. Height, current body mass index (BMI) and breast cancer risk

Variable	Premenopausal women			Postmenopausal women ¹⁾		
	Case No.	Control No.	OR ²⁾	Case No.	Control No.	OR ³⁾
Height						
< 155	11	14	1.00	18	22	1.00
155 - 165	43	48	1.08 (0.53 - 2.11) ⁴⁾	27	27	1.11 (0.34 - 2.01)
> 165	6	5	1.49 (0.63 - 2.71)	3	5	0.86 (0.39 - 3.03)
Body mass index (BMI)						
< 20	11	15	1.00	7	9	1.00
20 - 25	28	31	1.01 (0.29 - 2.19)	18	19	1.12 (0.75 - 2.06)
25 - 30	13	14	1.19 (0.59 - 2.03)	15	21	0.98 (0.41 - 1.96)
> 30	8	7	1.40 (0.55 - 2.99)	8	5	1.98 (1.08 - 2.05)*

1): This category included only natural menopause women

2): Odds ratio in premenopausal women adjusted for age

3): Odds ratio in postmenopausal women adjusted for age

4): 95% Confidence Interval (CI) * : $p < 0.05$

higher risk (OR = 1.98, 95% CI = 1.08–2.05) compared to women with indices below 20.

2. Breast feeding and breast cancer risk

Table 5 displays the risk of breast cancer associated with lactation as menopausal status. Odds ratio for those with a history of breast feeding compared with those who had never breast-fed was low (OR = 0.37, 95% CI = 0.25–0.89) and this association was shown only in premenopausal women. For risks associated with total periods of breast feeding, premenopausal women had lactated for total ≥ 36 months showed the lowest risk of breast cancer (OR = 0.28, 95% CI = 0.39–0.92) compared with women who had never breast-fed. The association between months of breast feeding of the first child and breast cancer also differed according to menopausal status. For premenopausal women, as compared with women had no breast feeding experience, women who had lactated ≥ 12 months to the first child showed a significantly lower risk (OR = 0.53, 95% CI = 0.24–0.97). In our data, the odds ratio for breast feeding was reduced among only premenopausal women who had ≥ 36 months

total duration of lactation, and ≥ 12 months lactation to the first child. However, results from postmenopausal women were not associated with decreased breast cancer risk.

DISCUSSION

Over the past decade, the relation of breast feeding to the risk of breast cancer has been studied extensively. A number of epidemiological studies have reported a reduced risk of breast cancer among women who have lactated.³⁻⁴⁾ As reported by other investigators, an independent protective effect of lactation was observed in some, but not all.⁵⁻⁶⁾ Although lactation has been regarded as important because its length is associated with the number of full-term pregnancies, biological mechanism about this issue contributes to be as controversial as ever. Protective effect of breast feeding was different as to menopausal status, and the larger protective effect was shown in premenopausal effects.⁷⁻⁸⁾ Breast feeding suppress ovulation, and there may be a direct relation between the lifetime number of ovulatory cycles and breast cancer risk.¹⁵⁾ Thus, the total duration of breast feeding might be inversely related to breast cancer risk. This paper confirmed an independent protective effect of breast feeding against the risk of breast cancer in Korea. In analysis, it is very important to control confounding factor because those factors are interrelated. Regression adjustment for confounding effects are necessary for unbiased results. Therefore, simultaneous adjustment for age, parity, and menopausal status, and body mass index were done in this study. In our results, lactation effect against breast cancer was associated with only premenopausal women. We found evidence that the longer the total duration of breast feeding, the lower the risk of breast cancer among women who had been pregnant. The risk of breast cancer were reduced only among premenopausal women with ≥ 12 months lactation to the first child. However, in our data, lactation was not related to breast cancer risk among postmenopausal women. From reports in oriental nations including Japan, it is clear that a positive history of breast feeding, as well as its duration, has an independent protective effect against breast cancer.⁹⁾ Romieu *et al.*,¹⁴⁾ reported an odds ratio of 0.28 (95% CI = 0.17–0.47) for those who breast-fed for ≥ 13 months compared with women who never breast-fed. Some studies found that breast cancer risk was reduced only among premenopausal women.^{4,16-17)} According to results about duration of lactation to the first child, Byers *et al.*,⁷⁾ reported odds ratios of 0.65 for premenopausal women who breast-fed

Table 5. Odds ratio (OR) of breast cancer in relation to breast feeding among parous women

Variable	Premenopausal women			Postmenopausal women ¹⁾		
	Case No.	Control No.	OR ²⁾	Case No.	Control No.	OR ³⁾
History of breast feeding						
Never	10	8	1.00	6	7	1.00
Ever	34	48	0.37 (0.25–0.89) ^{3)*}	38	44	0.91 (0.74–2.93)
Total periods of breast feeding (total month) ⁵⁾						
None	10	8	1.00	6	7	1.00
≤ 12	7	5	1.28 (0.46–2.47)	7	9	0.94 (0.96–2.93)
13–35	19	22	0.59 (0.45–3.49)	13	4	1.01 (0.57–2.13)
≥ 36	8	13	0.28 (0.39–0.92)*	18	21	0.85 (0.51–2.03)
Months of breast feeding to the first child						
None	10	8	1.00	6	7	1.00
≤ 3	7	10	0.97 (0.32–2.47)	8	6	1.08 (0.49–2.34)
4–11	15	17	1.03 (0.89–1.34)	20	22	1.19 (0.57–3.01)
≥ 12	10	19	0.53 (0.24–0.97)*	10	16	0.76 (0.32–1.68)

1): This category included only natural menopause women

2): Odds ratio in premenopausal women adjusted for age, age at menarche, and family history of breast cancer

3): Odds ratio in postmenopausal women adjusted for age, and body mass index

4): 95% Confidence interval (CI)

5): Only among women who ever pregnant * : $p < 0.05$

their first child 7–11 months and 0.24 for those who did it for ≥ 12 months compared with women who had never breast-fed. These results are very similar to our data. Some reports have shown an independent protective effect in parous women regardless of menopausal status.¹⁷⁻¹⁸ However, others found no relation between breast cancer risk and lactation,^{19,20} and there was a report from a breast cancer prevention program in Italy that did not find any protective effect.²¹ But it did not control any statistical adjustment for confounding factors. Other results from studies in Korea conducted in 1993 showed the independent protective effect of breast feeding.²²

There are several hypotheses to explain the mechanism for the effect of lactation has on the breast. One possible mechanism is that pregnancy and lactation may induce differentiation of the breast tissue, making it resistant to carcinogenesis.²³ Another suggestion is that, breast feeding causes reduced exposure to the hormones of menstruation because it is associated with amenorrhea. There are also some interesting results which show that the level of cholesterol β -epoxide, potential carcinogen, is lower in women during lactation and for up to 2 years after lactation.²⁴ Thus it is believed that breast feeding may reduce the exposure to potential carcinogen.

In interpreting of the results of our data, the bias relevant to case-control study needed to be taken into account. Perhaps the limitation of our study is that there was no community-based control group. Also, the issue of bias arises owing to a limited number of cases and controls. Therefore further study with a greater number of subjects should be conducted to evaluate the breast cancer risk and breast feeding among parous women. To overcome the recall bias in this study, lactation history questionnaire, including other variables, were done by a trained interviewer, and subjects were asked for the specifics of reported data (ex. marriage date, date of delivery, date of menarche etc.). Our study results support the hypothesis that lactation reduces breast cancer risk. Particularly notable thing was that a significant association of decreasing risk of breast cancer with increasing total duration of breast feeding, and ≥ 12 months of breast feeding to first child in premenopausal women. These findings suggest that evasion of breast feeding may have played a role in increasing breast cancer cases in Korea. Further comprehensive study with laboratory examination on hormones, in addition to a well constructed cohort study, is needed to assess lactation's relation to breast cancer.

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