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Menstrual and Reproductive Factors Related to the Risk of Breast Cancer in Korea

– Ovarian hormone effect on breast cancer –

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To support the ovarian hormone hypothesis in the etiology of breast cancer, a hospital-based case-control study with community controls was conducted to evaluate the relationship of intervals among menstrual and reproductive events to the risk of breast cancer in Korea. The cases were 190 breast cancer patients, who had been histologically diagnosed at Seoul National University Hospital from Jan. 1, 1993 to Jun. 30, 1994. Included were cancer-free women, who had undertaken the Gynecological examination at the same hospital (n=190). Women recruited for a survey of diabetes prevalence in Yonchon County, adjacent to Seoul City, were taken as a community control group (n=190). Information on menstrual and reproductive factors with other life-styles was collected through a direct interview by the well-trained interviewers. The adjusted odds ratios and the 95% confidence intervals were based on the unconditional logistic regression model. Likelihood ratio test for trend was applied for the ordinal variables. Early age at menarche, late age at natural menopause, late age at first full term pregnancy, and fewer number of full term pregnancies are independently associated with the high risk of breast cancer in Korea. Moreover, the interval between the age at menarche and the age at natural menopause of community controls (29.9±6.15 years) was significantly shortened compared to breast cancer cases (34.9±4.42 years). Particularly noteworthy was that intervals between the age at menarche and the age at first full term pregnancy of both control groups (9.0±3.72 years for hospital controls; 7.2±4.04 years for community controls) were significantly shortened compared to breast cancer cases (11.0±4.51 years). These findings support the hypothesis that the longer exposure to ovarian hormones during the reproductive years, the higher the risk of breast cancer.

Key Words : *Breast neoplasms, Menstrual factors, Reproductive factors, Risk*

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INTRODUCTION

The biology of breast cancer is not well understood and is undoubtedly complex (Kelsey, 1993). Early age at menarche, late age at menopause, nulliparity, and late age at first full term pregnancy with the increased risk of breast cancer, have been known for many years to be associated with the increased risk of breast cancer (Kelsey et al., 1993). But the evidence is overwhelming that ovarian hormones are one key factor in carcinogenesis of breast cancer. Thus, total exposure to both estradiol and progesterone during the reproductive years had been hypothesized to be of considerable potential risk factors for breast cancer (Henderson et al., 1982 ; Kelsey et al., 1993 ; Pike et al., 1993).

Breast cancer is one of the most common female cancers in Korea (Ministry of Health and Social Welfare, 1991-1992 ; Kim et al., 1995). Age-adjusted mortality and morbidity rates for breast cancer have been overwhelmingly increasing since 1980, suggesting that some underlying factors of breast cancer may exist in the population (Yoo and Kim,1992). Epidemiologic studies have suggested that such increase might be associated with changes in dietary factors (Yoo et al., 1993), improvement of anthropometric measures (Yoo, 1993), and postmenopausal obesity in this country (Joo el al., 1994).

Based on the previous epidemiological studies, early age at menarche, late age at menopause, nulliparity, late age at first pregnancy, and evasion of breast feeding have been known to be associated with an increased risk for breast cancer in Asian countries, including Korea (Hirohata et al., 1985 ; Tao et al., 1988 ; Yuan et al., 1988 ; Yoo et al., 1992a ; Yoo et al., 1995). However, the relationship between the duration of potential exposure to the ovarian hormones estrogen and the risk of breast cancer, to support the sex-hormone hypothesis, has been little investigated.

This hospital-based case-control study with community controls was conducted to investigate the relationship between the duration of potential exposure to the ovarian hormones estrogen and the risk of breast cancer in Korea.

MATERIALS AND METHODS

Study Population Incident cases were 190 breast cancer patients, who had been histologically diagnosed at Seoul National University Hospital from Jan. 1, 1993 to Jun. 30, 1994. For the hospital controls, women, who had taken part in the gynecological screening program at Seoul National University Hospital during the same period, were eligible. Among the eligible controls (n= 838), women with self-reported history of malignancies, tuberculosis, thyroid diseases, and diabetes, and women who had undertaken hysterectomy or oophorectomy, postmenopausal women due to surgical or drug-induced reason, and women with missing information on date of birth were deleted. Of the 580 potential controls, a hospital-control group was selected through a frequency matching procedure by PC-SAS (SAS Institute Inc. SAS/STAT user's guide, release 6.03 edition., 1988), permitting 5-year age intervals (n=190). To assess the potential selection bias in a hospital-based case-control study, a community control group was taken from women who had participated in a cross-sectional survey for diabetes prevalence in Yonchon County, located adjacent to Seoul City. Of the potential controls (n=1,407), women, who met the same exclusion criteria with the hospital controls, were deleted. The community controls (n=190) were selected from the potential controls by the same matching procedure with 5-year age interval (n=1,131). Repeated random selection procedures had been done to ensure the consistency of the age distribution of the selected samples to the remaining population (Table 1).

Information on menstrual and reproductive factors with other life-styles was obtained through a direct

Table 1. Socio-demographic characteristics of the study population interviewed in a hospital-based case-control study with community controls on breast cancer risk factors, 1992-1994, Korea

Demographic characteristics	No. of cases	No. of controls	
		hospital	community
Total	190(100)	190(100)	190(100)
Age at interview (years)			
30-34	10(5)	10(5)	10(5)
35-39	26(14)	26(14)	26(14)
40-44	45(24)	45(24)	45(24)
45-49	42(22)	42(22)	42(22)
50-54	25(13)	25(13)	25(13)
55-59	23(12)	23(12)	23(12)
60-64	13(7)	13(7)	13(7)
65+	6(3)	6(3)	6(3)
Occupation			
housewives	136(72)	147(77)	101(53)
all others	54(28)	43(23)	89(47)
Educational attainments			
below high school	134(71)	156(85)	158(85)
over college	55(29)	28(15)	29(16)
Body mass index (kg/m^2)a			
<20.0	26(15)	28(15)	18(10)
20.0-22.4	50(29)	57(30)	39(20)
22.5-24.9	46(26)	57(30)	48(26)
25.0+	53(30)	47(25)	82(44)

( ) : per cent to total.
[a] Weight/height^2.

interview by the well-trained interviewers. Contained in the questionnaire were socio-demographic pictures, past medical history, past history of malignancies, current height and current weight, smoking and alcohol drinking habits, and physical activities. Reproductive history with menstruation profile, i.e., age at menarche, menopausal status, age at natural menopause, age at first full term pregnancy, and the number of first full term pregnancies, was also obtained through the questionnaire. Body mass index was calculated as follows ; current weight/current height (Kelsey et al., 1993).

Statistical Analysis

Univariate analysis was done with the categorized variables as follows ; age at interview (30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65 or more), occupation (housewives, all others), educational attainments (below high school, college and the above), body mass index (below 20.0, 20.0-22.4, 22.5-24.9, 25.0 or more), age at menarche (below 14, 15-16, 17 or more), age at natural menopause among the postmenopausal women (below 44, 45-49, 50 or more), age at first full term pregnancy (below 24, 25-29, 30 or more), the number of full term pregnancies among the parous women (1, 2, 3, 4, 5 or more).

In order to assess the relationship between the duration of potential exposure to the ovarian hormones and the risk of breast cancer, the intervals among various menstrual and reproductive events were calculated as follows; interval between age at menarche and age at natural menopause among postmenopausal women, and the interval between age at menarche and age at first full term pregnancy among parous women.

Cases were compared to each control group, i.e., cases versus hospital controls, cases versus community controls, using the unconditional multiple logistic regression model. Covariates were age at interview, occupation, educational attainments, family history of breast cancer, past history of benign breast diseases, body mass index, and the history of full term pregnancy in the model to estimate the coefficients for the menstrual risk factors. Age at menarche and menopausal status, except for the ever having history of a full term pregnancy, were added to the previous model in the analysis of reproductive risk factors. To control the matching variable, we introduced an indicator variable of age at interview in all the logistic regression models (Breslow and Day, 1980 ; Holford, 1984).

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the menstrual and reproductive risk factors were based on the unconditional logistic regression model. Likelihood ratio test for the trend was applied for ordinal variables (Breslow and Day, 1980 ; Holford, 1984 ; Hosmer and Lemeshow, 1989).

Age at first full term pregnancy was defined as the age of the women at the ending date of her first pregnancy which extended into the third trimester, regardless of the outcome. Analysis on age at natural menopause, and the intervals between age at menarche and age at natural menopause were confined to the postmenopausal women, while the analysis on the reproductive variables, including intervals between age at menarche and age at first full term pregnancy, was restricted to the parous women. For the multivariate analysis, missing values for a small number of unknown categorical variables were imputed with age-stratum specific mode values. EGRET systems were used for the multivariate analysis (Statistics and Epidemiology Research Corporation.,1988).

Because the results from conditional logistic regression analysis due to age-matching did not show any difference, results from unconditional logistic regression analysis are, herewith, presenting.

RESULTS

Table 2 summarizes the adjusted odds ratios of menstrual and reproductive risk factors related to the breast cancer in Korea.

Compared to the hospital controls, the breast cancer risk decreased with age at menarche increasing (P_{trend} = 0.10). However, such tendency was more striking when compared to the community controls (P_{trend} = 0.00).

The likelihood ratio test for trend to assess a dose-dependent relationship between age at natural menopause and the breast cancer risk was statistically non-significant (P_{trend} = 0.19), when compared to the hospital control groups. However, the later the age at natural menopause, the higher the risk of breast cancer, when compared to the community controls (P_{trend} = 0.01). The breast cancer risk of women who had undertaken her menopause at age 50 or more was more than 6 times higher than women with the age of natural menopause at age below 44 (OR=6.34, 95% CI=1.49-27.0).

The breast cancer risk significantly increased with age at first full term pregnancy increasing (P_{trend} = 0.00, when compared to the hospital controls ; P_{trend} = 0.00, when compared to the community controls).

Table 2. Adjusted odds ratio and 95% confidence intervals of menstrual and reproductive factors related breast cancer risk among 190 breast cancer cases, 190 hospital controls, and 190 community controls interviewed in a case-control study, 1992-1994, Korea

Risk factors	No. of cases	No. of hospital controls	Odds ratio[a] (95% CI)	No. of community controls	Odds ratio[a] (95% CI)
Age at menarche					
≤14	74	53	1.0	30	1.0
15-16	71	81	0.83(0.49-1.38)	70	0.31(0.17-0.56)*
≥17	37	54	0.61(0.33-1.11)°	80	0.16(0.08-0.31)**
			P_{trend}[b]=2.63°		P_{trend}[b]=30.8**
Age at natural menopause[c]					
≤44	4	7	1.0	22	1.0
45-49	12	14	1.60(0.25-10.1)	29	2.23(0.50-10.1)
≥50	31	45	0.79(0.14-4.44)	21	6.34(1.49-27.0)*
			P_{trend}[b]=0.65		P_{trend}[b]=7.67*
Age at first full term pregnancy[d]					
≤24	67	95	1.0	122	1.0
25-29	90	81	1.65(1.01-2.70)*	45	3.66(2.12-6.32)**
≥30	23	7	4.11(1.56-10.9)**	9	3.41(1.32-8.80)**
			P_{trend}[b]=9.69**		P_{trend}[b]=19.7**
Number of full term pregnancies[d]					
1	24	11	1.0	10	1.0
2	84	56	0.73(0.31-1.73)	44	0.51(0.20-1.29)
3	45	59	0.29(0.11-0.72)**	46	0.21(0.07-0.57)**
4	18	35	0.13(0.04-0.37)**	38	0.10(0.03-0.29)**
≥5	9	22	0.10(0.03-0.33)**	38	0.03(0.01-0.12)**
			P_{trend}[b]=28.0**		P_{trend}[b]=43.2**

a : Adjusted odds ratios and 95% confidence intervals were based on coefficients and standard errors of the unconditional logistic regression models. Potential confounding effects by covariates ; age at interview, occupation, educational attainments, family history of breast cancer, past history of benign breast diseases, body mass index, and the history of ever had a full term pregnancy was adjusted in the model for the menstrual risk factors. Age at menarche and menopausal status, except the history of ever had a full term pregnancy, were added to the previous model in the analysis on reproductive risk factors.

b : The chi-square p-values from likelihood ratio tests for trend to assess the linear increase in the logit risk with exposure to the risk factor (d.f.=1).

c : Among postmenopausal women. d : Among parous women.

Table 3. Comparison of mean duration in years among age at menarche, age at first full term pregnancy, and age at natural menopause among 190 breast cancer cases, 190 hospital controls, and 190 community controls interviewed in a case-control study, 1992-1994, Korea

Duration between menstrual indicators	Cases	Hospital controls	Community controls
	Mean SD	Mean SD	Mean SD
Intervals between age at menarche and age at natural menopause[a]			
	34.9 ± 4.42	33.6 ± 3.82	29.9 ± 6.15**
Intervals between age at menarche and age at first full term pregnancy[b]			
	11.0 ± 4.51	9.0 ± 3.72**	7.2 ± 4.04**

a) Postmenopausal women b) Parous women ** $p < 0.01$, when compared to the value in the case group.

Women, who had their first full term pregnancy at age over 30, have a three to four times higher risk of breast cancer than women with their first full term pregnancy at age under 24. A linear decreasing trend in the breast cancer risk was apparently observed with the number of full term pregnancies increasing (P_{trend} =0.00, when compared to the hospital controls ; P_{trend} =0.00, when compared to the community controls).

Women with the child-bearing history of more than three children have less than a half risk of breast cancer compared women, who had only one child (Table 2).

Table 3 shows the results on comparison of mean duration in years among three variables ; age at menarche, age at first full term pregnancy and age at natural menopause. As can be seen in the table, the interval between the age at menarche and the age at natural menopause of community controls (29.9±6.15 years) was significantly shortened compared to breast cancer cases(34.9±4.42 years).

Particularly noteworthy was that the intervals between the age at menarche and the age at first full term pregnancy of both control groups (9.0±3.72 years for hospital controls ; 7.2±4.04 years for community controls) were significantly shortened compared to breast cancer cases (11.0±4.51 years).

DISCUSSION

This study confirmed that early age at menarche, late age at natural menopause, late age at first full term pregnancy, and fewer number of full term pregnancies are independently associated with the high risk of breast cancer in Korea. Moreover, the interval between the age at menarche and the age at natural menopause of community controls was significantly shortened compared to breast cancer cases. Particularly noteworthy was that intervals between the age at menarche and the age at first full term pregnancy of both control groups were significantly shortened compared to breast cancer cases.

To assess the potential selection bias in estimating the measure of association, a community control group was taken from women, who had participated in a cross-sectional survey (Schlesselman, 1982 ; Elwood, 1992 ; Laskey and Stolley, 1994). A cluster random sampling has been done to get a sample representative to the eligible population of adults over 20 years old in Yonchon County, which is half urban and half rural. The community controls were then selected by frequency matching from the population (Park et al., 1995).

Therefore, it is highly unlikely that the community controls for this analysis could be selectively biased to the eligible population in the cross-sectional survey. Although a different questionnaire was used to obtain information on life-style in the cross-sectional survey, the question items and its basic structure about both reproductive factors and other covariates were identical to the questionnaire used in this study. Moreover, the fact that the odds ratio and the mean value of each menstrual and reproductive history did not differ from the values of both hospital controls and community controls may favor, to a certain extent, an unbiased selection of the control group.

Potential confounders, which may distort the genuine relationship between menstrual and reproductive factors and the breast cancer risk, were selected from the previous epidemiologic studies (Hutchinson et al., 1980 ; Brinton et al., 1982 ; Lubin et al., 1985 ; Dupont and Page, 1987 ; London et al., 1989 ; La Vecchia et al., 1992 ; Tonkelaar et al., 1992 ; Kelsey, 1993 ; Yoo, 1993 ; Joo et al., 1994 ; Hirose et al., 1995). Current age (Kelsey, 1993 ; Yoo, 1993), occupation (Kelsey, 1993 ; Yoo, 1993), educational attainments (La Vecchia et al., 1992 ; Kelsey, 1993 ; Yoo, 1993), family history of breast cancer (Brinton et al., 1982 ; Dupont and Page., 1987 ; Kelsey, 1993 ; Hirose et al., 1995), past history of benign breast diseases (Hutchinson et al., 1980 ; Kelsey, 1993 ; Hirose et al., 1995), and the body mass index (Lubin et al., 1985 ; London et al., 1989 ; Kelsey et al., 1993 ; Tonkelaar et al., 1992 ; Joo et al., 1994 ; Hirose et al., 1995) were introduced to the model to control for the potential bias. Variables on both menstrual factors and reproductive factors were exclusively incorporated into the model in order to build a biologically plausible model. Since bilateral oophorectomy before age 40 may confer a lifelong reduction in the breast cancer risk about 45-50 percent (Brinton et al., 1988 ; Irwin et al., 1988), the surgically or iatrogenically induced postmenopausal women were excluded in this analysis.

As summary of the present study, early age at menarche, late age at natural menopause, late age at first full term pregnancy, and fewer number of full term pregnancies are independently associated with the high risk of breast cancer in Korea. The age at menarche and the age at menopause has been known for many years to be associated with increased risk of breast cancer (Paffenbarger et al., 1980 ; Byers et al., 1985 ; Hislop et al., 1986 ; Brinton et al., 1988 ; Yuan et al., 1988 ; Kelsey et al., 1993). The risk of breast cancer decreased with increasing age at menarche, and increased with increasing age at menopause in a prospective study of 63,090 Norwegian women, 1961-1980 (Kvale and Heuch, 1988). An international case-control study revealed that the younger a woman is at menarche, and the older a woman is at menopause, the higher her risk of breast cancer (Hsieh et al., 1990). However, the case-control studies from Japan (Hirohata et al., 1985 ; Yoo et al., 1992b ; Hirose et al., 1995), China (Tao et al., 1988), southern Europe (Brignone et al., 1987), and one report from Brazil (Gomes et al.,

1995) have found no relationship between the age at menarche and the breast cancer risk. If recall of age at menarche may be biased to the negative results, particularly for older women, the present results suggest that age at menarche is a stronger risk factor for breast cancer. Since menarche at a younger age is associated with earlier onset of regular menstrual cycles, early exposure to hormonal milieu associated with regular ovulatory cycles may be an important etiologic factor (Henderson et al., 1982 ; Pike et al., 1993).

Among postmenopausal women, the association of late menopause with the breast cancer risk was not seen in comparison with hospital controls. However, a linear relationship between age at menopause and the breast cancer risk was observed, when the breast cancer cases were compared to the community controls. Several studies on the relationship between age at menopause and the breast cancer risk showed inconsistent results, ranging from a negative (Yuan et al., 1988 ; Yoo et al., 1992b ; Gomes et al., 1995) or a weak association (Brignone et al., 1987 ; Tao et al., 1988) to a definite relationship with the breast cancer risk (Kvale and Heuch, 1988 ; Hsieh et al., 1990). Such negative results may be due to the different age distribution in case group, since the increased risk associated with late age at natural menopause is generally not seen until after age 65, suggesting that the effect of age at menopause is not seen for 10-20 years after menopause (Kelsey et al., 1993).

The increased risk of breast cancer with late age at first full term pregnancy among parous women was observed in the present study. The breast cancer risk decreased with the number of full term pregnancies increasing. Most of the epidemiologic studies have found that the younger a women is when she had her first full term pregnancy, the lower is her risk of breast cancer (Hirohata et al., 1985 ; Brignone et al., 1987 ; Yuan et al., 1988 ; Layde et al., 1989 ; Yoo et al., 1992a ; Hirose et al., 1995). However, other studies did not report a significant association (Rosero-Bixby et al., 1987 ; Tao et al., 1988 ; Gomes et al., 1995).

Although MacMahon et al. (1970) have found that high parity did not reduce the risk when age at first birth was taken into account, there was an independent protective effect of high parity against breast cancer in this study. Increased risk of breast cancer with age at first full term pregnancy was also independent of parity.

In the comparison of mean duration in years among age at menarche, age at first full term pregnancy and age at natural menopause, the interval between the age at menarche and the age at natural menopause of community controls was significantly shorter compared to breast cancer cases. Particularly noteworthy was that intervals between the age at menarche and the age at first full term pregnancy of both control groups were significantly shorter compared to breast cancer cases in this study. In a case-control study in a southern European population, a significant trend in the interval between age at menarche and age at first birth was observed. With a reference level of an interval of five years or less, an interval of more than 20 years has an OR of 5.34 (Brignone et al., 1987). These findings suggest that the number of menstrual cycles, uninterrupted by a pregnancy, is related to the risk of breast cancer.

The biology of breast cancer is not well understood and is undoubtedly complicated, but the evidence is overwhelming that ovarian hormones are one key factor in carcinogenesis. Estrogens, particularly estradiol, alone induce some cell division, but estradiol and progesterone together appears to induce more cell division. Thus, exposures associated with elevated levels of both estradiol and progesterone, may be of considerable interest as potential risk factors for breast cancer (Henderson et al., 1982 ; Kelsey, 1993 ; Kelsey et al., 1993 ; Pike et al., 1993). The findings in this study support the hypothesis that the longer exposure to ovarian hormones during the reproductive years, the higher the risk of breast cancer.

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