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Risk Factors for Breast Cancer: A Case-Control Study

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A hospital based case-control study was carried out to identify reproductive risk factors for breast cancer. Four-hundred-eighty-one breast cancer patients and 491 age-matched control patients examined between 1988 and 1994 were included in this study. Eleven reproductive risk factors were selected for comparison using cross tabulation and chi-square method, and univariate and multivariate logistic regression analyses were used to evaluate the odds ratios for the risk of breast cancer. The mean age of the breast cancer patients in this study was 47.5 years. Analyses demonstrated that nulliparous women had a higher risk for breast cancer (odds ratio 3.46, p=0.03) than women with 1-4 live births, and women who had an abortion during their first pregnancy had a slightly increased risk (odds ratio 1.86, p<0.01) than women who had normal deliveries, but the age at menarche and menopause did not have any influence on the risk of developing breast cancer. Although there were similarities in risk factors between Western women and women in this study, such as a higher risk for nulliparous women, two key factors were found to contrast with those of Western women. First, the mean age of breast cancer patients in this study was only 47.5 years. Second, the age of menarche and menopause of these women did not have any influence on the risk of breast cancer. **(Korean J of Breast Cancer 1998;1:109~118)**

Key Words: Breast cancer, Reproductive risk factors, Korean women

Introduction

Many risk factors for breast cancer have been found and many of them are recognized as established factors, at least in the Western hemisphere. Reproductive factors and the patients' age are probably among the most important risk factors.

Shapiro and coworkers[1] in 1968 reported that excess of breast cancer occurred in women who had never been married, those who had no more than two pregnancies, those with an early menarche, and those with 30 or more years of menstrual activity. Then in 1970, by a seven-center collaborative study of MacMahon and coworkers[2], a late age at first full-term birth became a major reproductive risk factor for breast cancer. The relationship between age and breast cancer risk was first described by Clemmesen in 1948[3]. In the United States and most European countries, the risk of breast cancer increases rapidly with age during childbearing years and the rates continue to increase even after menopause although at a less rapid pace.

Accumulated data also suggests that there are international geographic variations in the incidence and mortality rates of breast cancer[4]. Due to the fact that the incidence rate of breast cancer for Korean women was reported to be 9.9 per 100,000[5], perhaps the lowest in the world, it is reasonable to assume that risk factors might be different for Korean women than those reported for women in the Western hemisphere. We carried out a hospital based

case-control study to identify reproductive risk factors for breast cancer in Taegu, Korea. Although the cases selected here may not be representative of all Korean women, the risk factors we may find from this specific group of women should give some insight as to the differences between risk factors for Western and Korean women.

Materials and Methods

Detailed data have been obtained by administering a questionnaire to women who have visited the Department of Surgery, Keimyung University Dongsan Medical Center (one of three major university hospitals serving a population of over 5 million people) in Taegu, Korea, where the national medical insurance program enables all citizens to receive equal medical care with minimum expense, with symptoms or concerns related to their breasts since July of 1988. Women entering the clinic filled in the questionnaire prior to their examination. These forms were then verified by the author during their interview and examination. Records of a total of 2,193 women had been accumulated by June 30, 1994. Of the 2,193 women, 524 were patients with histologically proven breast cancer. The remaining 1,669 patients included 948 women with no proven breast diseases and 731 women with benign breast diseases all of which were verified by medical history, physical examination, mammography and biopsy when necessary. From the available data, reproductive factors including age at menarche and menopause, number of pregnancies and live births, age at the time of first pregnancy and delivery, number of induced and spontaneous abortions, result of the first pregnancy, feeding method for babies, and duration of breast feeding were selected for this study. When there were any missing values for the factors selected, the case was removed and the remaining 481 patients with histologically proven breast cancer were chosen for the study. Since 948 women who were examined at the clinic did not have any proven breast diseases and the reasons for their visit to the clinic were for annual examination, fear of cancer, or physiological breast discomfort, we determined that they qualified as our control group. Of these 948 women, those with missing values for any of the factors selected were also removed from the study and the ages of the remaining women were matched with the ages of respective patients with breast cancer (plus or minus one year). The number of the control group then became 491.

The breast cancer patients and the control group were summarized by cross tabulations and statistically analyzed by chi-square methods. Univariate and multivariate logistic regression analyses were used to evaluate the odds ratios for the risks of breast cancer and the selection of independent variables was made by the forward stepwise method with a likelihood ratio[6]. The software used for these analyses was SPSS for MS Windows, Release 6.0[7].

Results

The age distribution of women in this study was comparable for the breast cancer cases and the cont-

Table 1. Age distribution of breast cancer patients, Taegu, Korea

Ages in years	Number of patients	%
Less than 29	9	1.9
30~39	85	17.7
40~49	187	38.9
50~59	155	32.2
60~69	38	7.9
70 or above	7	1.4
Total	481	100.0

Mean: 47.5, Mode: 48.0, Standard error: 0.422, Standard deviation: 9.260

Table 2. Comparisons between breast cancer patients and control group by cross tabulation and chi-square method

	Case (%)	Control (%)	Chi-square value	DF*	Significance
Age at menarche			1.24	2	0.54
13 or below	47 (9.8)	40 (8.2)			
14~17	329 (68.4)	333 (67.8)			
18~21	105 (21.8)	118 (24.0)			
Age at menopause			0.50	2	0.78
Not reached	289 (60.1)	305 (62.1)			
21~49	105 (21.8)	99 (20.2)			
50 or above	87 (18.1)	87 (17.7)			
No. of pregnancies			16.75	3	<0.01
Nulliparous	39 (8.1)	11 (2.2)			
1~4	136 (28.3)	157 (32.0)			
5~9	262 (54.5)	279 (56.8)			
10 or more	44 (9.1)	44 (9.0)			
No. of live births			31.56	2	<0.01
Nulliparous	69 (14.4)	20 (4.1)			
1~4	332 (69.0)	384 (78.2)			
5 or more	80 (16.6)	87 (17.7)			
Age at 1st pregnancy			17.67	4	<0.01
No pregnancy	39 (8.1)	11 (2.2)			
17~19	41 (8.5)	44 (9.0)			
20~24	257 (53.4)	286 (58.3)			
25~29	133 (27.7)	141 (28.7)			
30 or above	11 (2.3)	9 (1.8)			
Age at 1st live birth			32.65	4	<0.01
No live birth	69 (14.3)	20 (4.1)			
19 or below	23 (4.8)	23 (4.7)			
20~24	198 (41.2)	242 (49.2)			
25~29	165 (34.3)	184 (37.5)			
30 or above	26 (5.4)	22 (4.5)			
No. of induced abortion			2.54	3	0.47
None	128 (26.6)	110 (22.4)			
1~3	256 (53.2)	282 (57.4)			
4~6	74 (15.4)	75 (15.3)			
7 or more	23 (4.8)	24 (4.9)			
No. of spontaneous abortion			0.12	1	0.73
None	343 (71.3)	355 (72.3)			
1 or more	138 (28.7)	136 (27.7)			
Result of 1st pregnancy			27.33	2	<0.01
None	39 (8.1)	11 (2.2)			
Delivered	250 (52.0)	318 (64.8)			
Aborted	192 (39.9)	162 (33.0)			
Method of feeding			37.44	2	<0.01
Nulliparous	69 (14.3)	20 (4.1)			

Breast	388 (80.7)	459 (93.5)			
Formula	24 (5.0)	12 (2.4)			
Duration of breast-feeding			32.29	3	<0.01
None	101 (21.0)	41 (8.4)			
1~4 years	207 (43.0)	261 (53.1)			
5~9 years	107 (22.3)	120 (24.4)			
10 or more	66 (13.7)	69 (14.1)			

*DF, degree of freedom.

rol group. The proportions of cancer patients less than 29 years of age, 30~39, 40~49, 50~59, 60~69 and 70 or over were 1.9%, 18.5%, 38.5%, 31.9%, 7.9% and 1.5% of the total number, respectively. The age distributions, as well as the mean and mode of age for breast cancer patients are shown in Table 1. The mean age of breast cancer patients was 47.5±9.3 years with the mode being 48.0. The peak age reached between 40 and 49 and thereafter the number of breast cancer patients decreased quite dramatically in this study group.

Summarization of the data by cross tabulation and statistical analysis by chi-square tests between breast cancer patients and the control group for the reproductive factors are summarized in Table 2. Comparisons of these factors including number of pregnancies, number of live births, age at the time of the first pregnancy, age at the time of the first live birth, result of the first pregnancy (delivered or aborted), method of feeding (breast or formula), and duration of breast-feeding, showed statistically significant differences between the two groups. However, comparisons of age at the time of menarche, age at the time of menopause, and the number of induced and spontaneous abortions, showed no significant differences between the two groups. The mean ages at menarche for the cancer patients and the control group were 15.9±1.9 and 16.2±1.7 years, respectively (p=0.21), and the mean ages at menopause for the cancer patients and the control group were 47.5±6.1 and 47.8±5.8, respectively (p=0.58). Odds ratios were obtained by using univariate and multivariate logistic regression analyses. The results of the univariate analysis are summarized in Table 3 and the results of the multivariate analysis are summarized in Table 4.

The univariate logistic regression analysis showed that there was no significant difference in the odds ratios of the age at menarche, the age at menopause, and the number of induced and spontaneous abortions. The odds ratio was 3.99 ($p<0.01$) for nulliparous women when compared with women who had between one and four pregnancies and the ratio for nulliparous women was 4.14 ($p<0.01$) when compared with women who had one to four live births. However, for those women with one or more pregnancies or live births, the number of pregnancies orlive births did not have any influence on the risk of breast cancer. The ages at the time of the first pregnancy or at the time of the first live birth did not have any influence on the risk, but again nulliparous women had a significantly elevated risk of breast cancer when compared to women who had their first pregnancies between the ages of 20 and 24 (odds ratio=3.95, $p<0.01$) and women who had their first live births between these same ages (odds ratio=4.22, $p<0.01$). Women who aborted their first pregnancies (either induced or spontaneous) had an odds ratio of 1.51 ($p<0.01$) compared to women who delivered. Formula feeding resulted in an odds ratio of 2.37 ($p=0.02$) when compared with breast-feeding, and nulliparous women had an odds ratio of 4.23 (p<

Table 3. Summary of results of univariate logistic regression analysis of breast cancer

Variable ( )*	β**	S.E. (β)***	p value	Odds ratio
Age at menarche (14~17 years)*				
11~13	0.173	0.229	0.54	1.19
18~21	0.105	0.155	0.50	0.90
Age at menopause (50~59 years)*				
Not reached	-0.054	0.172	0.75	0.95
49 or less	0.588	0.206	0.78	1.06
Number of pregnancy (1~4)*				
None	1.383	0.362	<0.01	3.99
5~9	0.085	0.145	0.56	1.09
10 or more	0.144	0.243	0.56	1.15
Number of live births (1~4)*				
None	1.420	0.270	<0.01	4.14
5 or more	0.061	0.172	0.72	1.06
Age at first pregnancy (20~24 years)*				
Nulliparous	1.373	0.352	<0.01	3.9
17~19	0.031	0.241	0.90	1.03
25~29	0.049	0.148	0.74	1.05
30 or over	0.308	0.458	0.50	1.36
Age at first full term delivery (20~24 years)*				
Nulliparous	1.439	0.271	<0.01	4.2
18~19	0.201	0.310	0.52	1.22
25~29	0.092	0.144	0.52	1.10
30 or over	0.368	0.305	0.23	1.44
Number of induced abortions (None)*				
1~3	-0.248	0.156	0.11	0.78
4~6	-0.165	0.209	0.43	0.85
7 or more	-0.194	0.319	0.54	0.82
Number of spontaneous abortions (None)*				
1 or more	0.049	0.143	0.73	1.05
Result of first pregnancy (Delivered)*				
Nulliparous	1.536	0.351	<0.01	4.64
Aborted	0.415	0.136	<0.01	1.51
Baby feeding method (Breast-feeding)*				
Nulliparous	1.443	0.269	<0.01	4.2
Formula feeding	0.861	0.360	0.02	2.37
Duration of breast-feeding (1~4 years)*				
None	1.133	0.207	<0.01	3.10
5~9	0.117	0.162	0.47	1.12
10 or more	0.187	0.196	0.34	1.21

*( ), reference category; **β: coefficient; ***S.E.(β), standard error of coefficient.

0.01). Women who did not breast-feed had an odds ratio of 3.10 ($p<0.01$) when compared with women who had breast-fed for a period of one to four years. Longer duration of breast-feeding, however, did not

Table 4. Summary of results of multivariate logistic regression analysis of breast cancer

Variable ( )*	β**	S.E. (β)***	p value	Odds ratio
Number of live births (1~4)*				
Nulliparous	1.240	0.418	0.03	3.46
5 or more	-0.829	0.194	0.67	0.92
Result of first pregnancy (Delivered)*				
Nulliparous	0.641	0.556	0.25	1.90
Aborted	0.623	0.170	<0.01	1.86

*( ), reference category; **β, coefficient; ***S.E.(β), standard error of coefficient.

influence the odds ratio.

For the multivariate logistic regression analysis,age as well as the following variables which showed statistically significant differences in the univariate analyses were included: number of pregnancies, number of live births, age at first pregnancy, age at first live birth, result of first pregnancy, feeding methods, and duration of breast-feeding. The results showed that nulliparous women had an odds ratio of 3.46 (p=0.03) compared with women who had between one and four pregnancies, but for those who had one or more pregnancies, the number of pregnancies did not influence the odds ratio. Women who aborted their first pregnancy (either induced or spontaneous) had an odds ratio of 1.86 (p<0.01) compared to women who delivered with their first pregnancy.

Discussion

Many risk factors for breast cancer development have been described and some of them including age, family history of breast cancer, prior history of breast cancer, and reproductive factors are well established[8-11]. Age is a very important risk factor, especially in Western women. According to Osteen and Karnell[12], the average age of breast cancer patients was 61.1 years and more than three quarters of these women were 50 years of age or above in the United States. In Western women, most incidents of breast cancer occur during the postmenopausal years and the incidence of breast cancer increases, although somewhat more slowly, even after menopause[11,13-16]. In this study, the mean age of this group of Korean breast cancer patients was 47.5±9.3 years with the mode being 48.0. The peak age reached between 40 and 49 and thereafter the number of breast cancer patients decreased quite dramatically and only 41.1% (200/481) were 50 years old or above. No adequate explanation could be given for the younger age at the onset of the breast cancer in Korean women, although it is possible that the present trend is a temporary one and as the incidence of the breast cancer increases in the future, the age distribution may become similar to Western women.

Reproductive factors or endogenous endocrine factors are among the confirmed risk factors for breast cancer. The age at menarche, age at menopause, parity, age at the first full-term pregnancy, and total duration of menstruation are among these factors, all of which are important for Western women[10,17-20]. Earlier menarche was found in a statistically significant proportion of patients with breast cancer compared to control groups in many Western reports[21-23]. In this study, the average age at menarche for breast cancer patients and the control group was 15.9±1.9 and 16.2±1.7years, respectively (p=0.21). For Western women, the average age at menarche was reported to be around 13 in 1986 and was pro-

gressively declining at the rate of about four months per decade[14]. There was no evidence that the age at menarche was a risk factor in this case control study in Korean population but later age at menarche in Korean women in general might explain some of the difference in incidence rates between Korean and Western women. The average age at menopause for cancer patients and the control group was 47.5±6.1 and 47.8±5.8 years, respectively (p=0.58), therefore there was no evidence that the age at menopause contributed to the risk of breast cancer. The age at the time of the first full-term pregnancy was a very important risk factor for Western women[24-27]. Recently Kalache and coworkers[28] also reported that high breast cancer risk was associated with low parity and after adjustments for parity were made, breast cancer risk was related both to late age at first full-term pregnancy and to late age at last full-term pregnancy and the multivariate analysis revealed that the effect of age at last full-term pregnancy dominated that of age at first full-term pregnancy. Nulliparity has also been considered a risk factor by many studies[14,22,25,29], although the degree of risks involved differ somewhat. In this study, nulliparity was considerably more common among cancer patients. Women without any pregnancies reached 39 in number (8.1%) for cancer patients and 11 (2.2%) for the control group. The number of women without any live births was 69 (14.3%) for cancer patients and 20 (4.1%) for the control group. When women with one to four pregnancies were compared with women without any pregnancies, the odds ratio was 3.99 (p<0.01) in the univariate analysis, but the difference became unimportant in the multivariate analysis. For those with one or more pregnancies, the number of pregnancies did not have any significant difference. When women with one to four live births were compared with nulliparous women, the odds ratio was 4.14 (p<0.01) in the univariate analysis and the difference was significant even in the multivariate analysis (odds ratio 3.46, p=0.03). Women with one or more live births were also not affected by the number of live births. Furthermore, the age at the time of first pregnancy did not affect the risk for breast cancer for those who had one or more pregnancies but women without any pregnancies had an odds ratio of 3.95 (p<0.01) when compared with women who had their first pregnancy at an age between 20 and 24 in univariate analysis. For those who had first live births, the age at the time of delivery did not affect their risk, although women who have not had a live birth had an odds ratio of 4.22 (p<0.01). This comparison was made with women who had their first full-term delivery between the ages of 20 and 24 in the univariate analysis. However, both of these statistical significances disappeared in the multivariate analysis. Thus, nulliparity was an important risk factor for the breast cancer in Korean women as it was for Western women, but younger age at the time of first full-term pregnancy and the number of live births were not risk factors for Korean women in contrast to Western women. Younger age at the onset of the breast cancer suggested that reproductive factors might play a stronger role for Korean women, but the results were contrary and factors other than reproductive factors, such as dietary and environmental factors, might be more important as risk factor for the breast cancer.

A history of ever having a miscarriage was associated with some increase in risk in several studies[30,31]. Pike and co-workers[32] reported that a first trimester abortion prior to a full-term birth was associated with a twofold elevation in risk, but in other studies there was no excess risk associated with having a first trimester abortion prior to a full-term birth[33,34]. In this study, the number of induced abortions did not have any influence on the risk when compared with women with no induced abortions; also no relationship was present between those who had spontaneous abortions and those who did not

have any abortions. The result of the first pregnancy was significantly different between cancer patients and the control group. When women who delivered after their first pregnancy were compared with nulliparous women, the odds ratio was 4.64 ($p<0.01$), and when compared with women who aborted their first pregnancy, the odds ratio was 1.51 ($p<0.01$) in the univariate analysis. In the multivariate analysis, only women who aborted their first pregnancy had an odds ratio of 1.86 ($p<0.01$).

Since MacMahon and co-workers[2] published their international study, it was widely believed that lactation had no effect on the incidence of breast cancer independent of the association of a long total duration of lactation with an early age at the first full-term pregnancy, but Byers and co-workers[35] in 1985 reported that lactation may reduce the risk of breast cancer among premenopausal women. Furthermore, studies in China suggested that long-term lactation was protective and that the protection was probably not limited to premenopausal women[9]. Newcomb and co-workers[36] reported a slight protective effect associated with a longer duration of lactation in premenopausal women but not in postmenopausal women suggesting a stronger protective effect of lactation at early ages than at older ages. In this study, using the univariate analysis, nulliparous women had an odds ratio of 4.23 ($p<0.01$) when compared with women who breast-fed, and women who used formula had an odds ratio of 2.37 ($p=0.02$). This seemed to show a significant protective effect for breast-feeding, but the multivariate analysis did not show feeding methods to be a significant risk factor. The duration of breast-feeding was also not an important factor.

This study showed that nulliparous women had a higher risk of breast cancer (odds ratio 3.46, $p=0.03$) than women who had between one and four live births, and for women with one or more live births, the number of births did not affect their risk. Also, women who had an abortion during their first pregnancy, either spontaneous or induced, had a slightly increased risk (odds ratio 1.86, $p<0.01$) when compared to women who had normal deliveries. Finally, this study reports the two most contrasting factors to that of Western women. First, it is shown that the mean age of breast cancer patients in this study reached only 47.5 ± 9.3 years with the peak age being between 40 and 49 and thereafter the number of breast cancer patients decreased quite dramatically. And second, it is revealed that the age of menarche and menopause of these women did not have any influence on the risk of breast cancer.

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