Life-style in Relation to the Risk of Breast Cancer*

Keun-Young Yoo¹, Kazuo Tajima², Tetsuo Kuroishi², Kaoru Hirose²,
Shigeto Miura³, Hiroshi Murai³, and Minoru Yoshida³

1. *Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea*

2. *Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya, Japan*

3. *Department of Breast Surgery, Aichi Cancer Center Hospital, Nagoya, Japan*

A hospital-based case-control analysis was conducted to assess the relationship of life-style to breast cancer in Japan. The study population was selected among the outpatients of a hospital where information on life-style had been routinely collected prior to diagnosis since 1987. The age-adjusted risk to breast cancer significantly decreased with marital status, full-term pregnancy history, number of fullterm pregnancies, number of breastfed children, and the average length of breastfeeding, while age at first fullterm pregnancy and family history of breast cancer were positively associated with the risk. The adjusted risk, controlling for potential confoundings, significantly decreased in alcohol drinkers. On the other hand, there was a significant dose-response gradient of increasing risk with smoking. No relationship of physical activity to the disease was observed. There were significant decreases in the risk with increasing intake of rice, bean curd, soy bean paste, and green vegetables. However, no evidence of increase in the risk was found with a high fat diet. These findings suggest that further study under the specific hypothesis in a different population should be followed to confirm the different risk factors of breast cancer in Oriental people from those in the Western countries.

Alcohol, Breast neoplasms, Dietary factors, Life-style, Reproductive factors, Physical activity, Risk, Smoking

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INTRODUCTION

Life-style associated with breast cancer encompasses menstrual and reproductive factors, and personal preference, for example, smoking and drinking habits. In addition, physical activities and dietary habits are some other factors. There is an abundance of epidemiological evidence that early menarche, late menopause, and delayed age at first delivery are closely related to breast cancer^(1,2). International similarity of these factors is more persuasive to the role of estrogen^(1,3), while other factors are still controversial. An examination of related factors, which would be heterogenous among different countries, is thus necessary for a further understanding of the etiology of cancer.

This is a hospital-based case-control analysis aimed at clarifying what kind of life-style is associated with the risk of breast cancer in Japan, where the incidence of and mortality rate due to breast cancer has recently been increasing⁽⁴⁾.

SUBJECTS

Information on life-style has been routinely collected from all the outpatients of the Aichi Cancer Center Hospital, Nagoya, Japan, since 1987. All data was obtained prior to diagnosis, through a self-administered questionnaire under the supervision of an interviewer. The study population was primarily sampled for a study on the comparison of risk factors between breast cancer and uterine cervix cancer, the results of which will be published elsewhere. Women who were newly diagnosed as breast cancer in this hospital, both histologically and clinically, were taken as the case group from January 1, 1988 to December 31, 1989. Six hundred seventy-seven controls were randomly selected among those having no evidence of any cancer in the hospital. No duplicate case, nor control, was permitted in this analysis. The cases were slightly older than the controls, but occupation and marital status did not significantly differ between the two groups (Table 1).

METHODS

All the variables on menstrual and reproductive factors, as well as variables on familial factors, were categorized in an ordinal scale. Information on both dietary habits and intake frequency was gathered through a self-administered questionnaire, in which the frequency of each item was classified in an ordinal scale with an increasing order.

For comparison with other results, relative risks of reproductive and familial factors in Table 2, 3, and 4 are presented as age-adjusted risks. For other variables on life-style, potential confounding effects by age, and reproductive and familial factors, either statistically significant or biologically plausible, were controlled by the unconditional logistic model.

Table 1 Characteristics of breast cancer cases and controls

Characteristics	Cases		Controls		Pearson's χ^2
	No.	%	No.	%	
Total	522	100.0	677	100.0	
Age in years					
- 19	0	0.0	7	1.0	
20 - 24	1	0.2	21	3.1	
25 - 29	5	1.0	31	4.6	
30 - 34	18	3.5	46	6.8	
35 - 39	42	8.1	87	12.9	
40 - 44	76	14.6	141	20.8	
45 - 49	96	18.4	132	19.5	93.8 (14) p=0.00
50 - 54	84	16.1	69	10.2	
55 - 59	64	12.3	56	8.3	
60 - 64	63	12.1	36	5.3	
65 - 69	34	6.5	24	3.6	
70 - 74	18	3.5	17	2.5	
75 - 79	16	3.1	7	1.0	
80 - 84	3	0.6	2	0.3	
85 -	2	0.4	1	0.2	
Occupation					
upper	239	45.8	320	47.3	
middle	66	12.6	79	11.7	3.97 (3) ns
lower	25	4.8	49	7.2	
unemployed	192	36.8	229	33.8	
Marital status					
single	35	6.8	55	8.2	0.82 (1) ns
married	481	93.2	617	91.8	

ns : p > 0.1

Table 2 Age-adjusted risk of breast cancer associated with reproductive factors among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Categories ¹⁾	Chi values for trend ²⁾
Marital status	single, married	-2.5, p=0.01
Age at menarche	-12, 13-14, 15-16	0.0, ns
Menstrual regularity	regular, irregular	-1.6, p=0.10
Menopausal status	pre-, postmenopause	0.1, ns
Age at natural menopause	pre-, -44, 45-49, 50-54, 55+	0.3, ns
Fullterm pregnancy history	nulli-, multiparous	-2.8, p=0.00
Age at first ³⁾ fullterm pregnancy	-19, 20-24, 25-29, 30-34, 35+	4.0, p=0.00
Number of fullterm pregnancies	nulli-, 1, 2, 3, 4+	-4.0, p=0.00

¹⁾Each category was coded in increasing order.²⁾The chi value, instead of chi-square, was presented to show both significance of the linearity and its direction. The value was drawn from the change in log-likelihoods between unconditional logistic model with and without the continuous variable.³⁾Result was derived from a data restricted to multiparous group.
ns : p > 0.1

Table 3 Age-adjusted risk of breast cancer associated with breastfeeding history among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Case Control		Adjusted RR ¹⁾ (95% CI)	X ² _{LR} ²⁾	X ² _{trend} ³⁾	X ² _{departure} ⁴⁾
Number of breastfed children						
0	133	146	1.0			
1	79	92	0.73 (0.48-1.10)	22.7(4)	21.6(1)	1.1(1)
2	208	281	0.60 (0.43-0.83)	p=0.00	p=0.00	ns
3	73	126	0.41 (0.27-0.61)			
4+	29	31	0.43 (0.23-0.80)			
Average lengths of breastfeeding (month)						
0	133	146	1.0			
1 - 3	84	133	0.62 (0.42-0.92)	18.4(5)	6.8(1)	11.6(4)
4 - 6	67	117	0.47 (0.31-0.71)	p=0.00	p=0.01	p=0.02
7 - 9	33	60	0.44 (0.26-0.74)			
10 - 12	171	180	0.62 (0.44-0.88)			
13+	33	40	0.53 (0.30-0.93)			

¹⁾Adjusted relative risk for age was derived from regression coefficient of unconditional logistic model. Its 95% confidence intervals were calculated by the logit method.

²⁾The likelihood ratio test for the null hypothesis: $\beta_{\text{ordinal}(i)} = 0$.

³⁾The chi-square due to linear regression under the null hypothesis:

$\beta_{\text{continuous}(1)} = 0$.

⁴⁾The chi-square due to the departure from the linearity; $X^2_{\text{departure}} = X^2_{\text{LR}} - X^2_{\text{trend}}$.

(): degree of freedom

ns : $p > 0.1$

Table 4 Age-adjusted risk of breast cancer associated with familial factors among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Categories ¹⁾	Chi values for trend ²⁾
Family history among first relatives	no, yes	1.7, p=0.09
Number of siblings	1-2, 3-4, 5-6, 7+	0.3, ns
Birth order	first, others	0.1, ns

¹⁾Each category was coded in increasing order.

²⁾The chi value, instead of chi-square, was presented to show both significance of the linearity and its direction. The value was drawn from the change in log-likelihoods between unconditional logistic model with and without the continuous variable.

ns : $p > 0.1$

Adjusted relative risks were calculated from the logistic regression equation^(5,6). The logit method was applied for 95% confidence limits of the adjusted risk⁽⁷⁾. A test for the null hypothesis that the ordinal variable had no effect on the disease, as well as the test for linear trend of the logit risk in each factor was done by the likelihood ratio test^(5,6,8). The X²_{trend} statistic was obtained from the change in scaled deviance; the difference in two log-likelihoods between a logistic model with and without the transformed continuous variable. For convenience, the chi-value, instead of chi-square, was presented to show implicatively both the significance of the linearity and its direction, which followed the normal distribution

(Table 2, 4, 7 & 8). Along with the test for trend, another chi-square, $X^2_{\text{departure}}$, was calculated to evaluate departure from the linearity⁽⁸⁾. All the statistical procedures were carried out using the PC-SAS⁽⁹⁾ and the GLIM system⁽¹⁰⁾. The critical level chosen for the statistical significance was 0.1.

Table 5 Alcohol drinking, smoking habits and the risk of breast cancer among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Case Control		Adjusted ¹⁾ RR(95% CI)	X ² _{LR} ²⁾	X ² _{trend} ³⁾	X ² _{departure} ⁴⁾
Alcohol drinking habit						
never	402	473	1.0			
ex-drinker	5	4	1.21 (0.27-5.34)	6.2(2)	5.9(1)	0.3(1)
drinker	114	200	0.69 (0.52-0.93)	p=0.05	p=0.01	ns
Alcohol drinking frequency						
never	403	473	1.0			
occasional	77	153	0.64 (0.46-0.89)	7.3(2)	2.4(1)	4.9(1)
daily	42	51	0.94 (0.59-1.51)	p=0.02	ns	p=0.02
Smoking habit						
never	435	583	1.0			
ex-smoker	18	17	1.58 (0.76-3.26)	6.2(2)	5.8(1)	0.4(1)
smoker	67	76	1.58 (1.06-2.35)	p=0.05	p=0.01	ns
Age at first smoking						
never	437	584	1.0			
age <19	10	11	2.04 (0.77-5.39)	5.0(3)	3.0(1)	2.0(2)
age 20-29	46	54	1.47 (0.94-2.31)	ns	p=0.08	ns
age 30-	28	25	1.26 (0.70-2.26)			
Average amount of cigarettes per day						
never	437	584	1.0			
less than 10	33	48	1.08 (0.65-1.78)	7.5(2)	6.6(1)	0.9(1)
more than 10	49	43	1.96 (1.21-3.18)	p=0.02	p=0.01	ns

¹⁾Adjusted relative risk was derived from regression coefficient of unconditional logistic model. Its 95% confidence intervals were calculated by the logit method. Adjustments were done for the following variables; age, marital status, number of fullterm pregnancies, average duration of breastfeeding, family history of breast cancer among first relatives. In addition, alcohol drinking habit and smoking habit were adjusted for each other, and alcohol drinking frequency and average amount of cigarettes per day were adjusted for each other.

²⁾The likelihood ratio test for the null hypothesis: $\beta_{\text{ordinal}(1)} = 0$.

³⁾The chi-square due to linear regression under the null hypothesis:

$\beta_{\text{continuous}(1)} = 0$.

⁴⁾The chi-square due to the departure from the linearity; $X^2_{\text{departure}} = X^2_{\text{LR}} - X^2_{\text{trend}}$.

(): degree of freedom

ns : $p > 0.1$

Table 6 Physical activities and the risk of breast cancer among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Case Control		Adjusted ¹⁾ RR(95% CI)	X ² _{LR} ²⁾	X ² _{trend} ³⁾	X ² _{departure} ⁴⁾
Sleeping time in hours						
- 5	35	37	1.0			
6 - 8	468	629	0.88 (0.53-1.47)	1.2(2)	0.0(1)	1.2(2)
9 -	18	11	1.38 (0.51-3.69)	ns	ns	ns
Physical activity						
active	199	285	1.0			
inactive	319	387	1.16 (0.90-1.49)	1.3(1), ns		

¹⁾Adjusted relative risk was derived from regression coefficient of unconditional logistic model. Its 95% confidence intervals were calculated by the logit method. Adjustments were done for the following variables; age, marital status, number of fullterm pregnancies, average duration of breastfeeding, and family history of breast cancer among first relatives.

²⁾The likelihood ratio test for the null hypothesis: $\beta_{ordinal(i)} = 0$.

³⁾The chi-square due to linear regression under the null hypothesis:

$\beta_{continuous(1)} = 0$.

⁴⁾The chi-square due to the departure from the linearity; $X^2_{departure} = X^2_{LR} - X^2_{trend}$.

(): degree of freedom

ns : $p > 0.1$

Table 7 Dietary habits and the risk of breast cancer among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Risk factors	Categories ¹⁾	Chi values for trend ²⁾
Kinds of breakfast	rice, bread, mixed, skip	1.5, ns
Number of rice bowl per day	half, 1-2, 3-4, 5+	-2.3, $p=0.02$
Hastiness in eating meal	slow, slightly slow, slightly fast, fast	-0.8, ns
Saltiness preference	like, moderately like, moderately dislike, dislike	-1.5, ns
Greasiness preference	like, moderately like, moderately dislike, dislike	-1.3, ns

¹⁾Each category was coded in increasing order.

²⁾The chi value, instead of chi-square, was presented to show both significance of the linearity and its direction. The value was drawn from the change in log-likelihoods between unconditional logistic model with and without the continuous variable.

ns : $p > 0.1$

Table 8 Food intake frequency and the risk of breast cancer among 1,199 Japanese women in the Aichi Cancer Center Hospital, Nagoya, Japan, during 1988-1989

Foods ¹⁾	χ^2_{LR} ²⁾	χ_{trend} ³⁾	$\chi^2_{departure}$ ⁴⁾
Fish	2.0(4), ns	-1.0(1), ns	0.9(3), ns
Salt fish	2.6(4), ns	1.0(1), ns	1.6(3), ns
Bean curd (tofu)	5.3(4), ns	-1.7(1), p=0.08	2.3(3), ns
Soy bean paste	8.0(3), p=0.04	-0.8(1), ns	7.4(2), p=0.02
Fruits	0.8(3), ns	-0.6(1), ns	0.4(2), ns
Chinese cabbage	4.5(4), ns	-0.7(1), ns	4.0(3), ns
Green vegetables	9.1(4), p=0.05	-2.4(1), p=0.01	3.1(3), ns
Carrot	4.6(4), ns	0.6(1), ns	4.2(3), ns
Pumpkin	3.6(4), ns	1.4(1), ns	1.7(3), ns
Cabbage	7.7(4), p=0.10	2.5(1), p=0.01	1.6(3), ns
Lettuce	4.0(4), ns	1.2(1), ns	2.6(3), ns
Potato	6.2(4), ns	-0.4(1), ns	6.0(3), ns
Egg	0.7(4), ns	0.5(1), ns	0.4(3), ns
Chicken	2.9(4), ns	0.3(1), ns	2.8(3), ns
Beef	1.4(4), ns	1.1(1), ns	0.2(3), ns
Pork	5.3(4), ns	0.3(1), ns	5.2(3), ns
Ham and sausage	2.7(4), ns	-0.5(1), ns	2.4(3), ns
Precooked noodle	1.2(4), ns	0.9(1), ns	0.3(3), ns
Milk	2.4(3), ns	0.6(1), ns	2.0(2), ns

¹⁾ Intake frequency of each food item (except soy bean paste, fruits, milk) was categorized as follows; 1 = seldom, 2 = 1-3 times/month, 3 = 1-2 times/week, 4 = 3-4 times/week, 5 = daily. For those of soy bean paste, fruits, and milk, 1 = seldom, 2 = occasionally, 3 = 3-4 times/week, and 4 = daily.

²⁾ Adjusted relative risk was derived from regression coefficient of unconditional logistic model. Its 95% confidence intervals were calculated by the Miettinen's test-based method. Adjustments were done for the following variables; age, marital status, number of fullterm pregnancies, average duration of breastfeeding, and family history of breast cancer among first relatives.

³⁾ The likelihood ratio test for the null hypothesis: $\beta_{ordinal(1)} = 0$.

⁴⁾ The chi-square due to linear regression under the null hypothesis:

$\beta_{continuous(1)} = 0$.

⁵⁾ The chi-square due to the departure from the linearity; $\chi^2_{departure} = \chi^2_{LR} - \chi^2_{trend}$.

(): degree of freedom

ns : p > 0.1

RESULTS

The age-adjusted risk of breast cancer associated with reproductive factors is summarized in Table 2. While age at menarche and natural menopause, menopausal status were not related with breast cancer, and while menstrual regularity showed borderline significance, the age-adjusted risk of breast cancer was significantly reduced with marital status, fullterm pregnancy history, number of fullterm pregnancies, number of breastfed children, and the average lengths of breastfeeding in month (Table 3). In contrast, age at first fullterm pregnancy and the family history of breast cancer among first relatives were positively associated with the risk. Neither the number of siblings nor birth order was related to the disease (Table 4).

There was a significant decrease in the risk of breast cancer associated with alcohol (Table 5). The biggest decrease in risk was seen among drinkers (adjusted RR = 0.69, 0.52–0.93). In spite of a nonlinear relationship ($X^2_{\text{departure}} = 4.9$, $df = 1$, $p = 0.02$), the risk among occasional drinkers decreased significantly (adjusted RR = 0.64, 0.46–0.89). Contrary to alcohol, a substantial increase in the risk among ex-smokers and smokers was observed ($X^2_{\text{trend}} = 5.8$, $df = 1$, $p = 0.01$). The age at first smoking showed an inverse relationship with breast cancer. While the risk of mild smokers (less than 10 cigarettes/day) was almost similar to that of non-smokers, there was an apparent increase in the risk among smokers (more than 10 cigarettes/day) (adjusted RR = 1.96, 1.21–3.18), with a significant dose-dependent gradient.

A nonsignificant association between the sleeping time and the risk of breast cancer was observed. Although the risk seemed to slightly increase in physically inactive women, it was also nonsignificant (Table 6).

Among dietary habits, the intake of rice at breakfast seemed to have a protective effect against breast cancer (Table 7). This was seen from the decreasing tendency in risk with the increase in number of bowls of rice/day ($X^2_{\text{trend}} = 5.1$, $df = 1$, $p = 0.02$). Hastiness in eating meals, or preference to saltiness or to greasiness, was not at all related to the risk of breast cancer.

The logit risk of breast cancer in Table 8 had a significant linear relationship with the intake frequency of green vegetables ($p = 0.01$), as well as of bean curd ($p = 0.08$). In spite of a nonlinear trend associated with soy bean paste ($X^2_{\text{departure}} = 7.4$, $df = 2$, $p = 0.02$), its direction was towards protection against breast cancer. Meanwhile, the intake of cabbage showed a significant increase in the risk. There was no positive evidence on the association between the intake of food containing high calories or fat and the risk of breast cancer in this population.

DISCUSSION

Although the incidence of female breast cancer in Oriental countries is still lower than that in Western countries, it is evident that the rate is increasing in several Asian countries^(4,11-13). Life-style associated with a disease may differ from country to country, and comparing these differences can sometimes provide important clues concerning the etiology of a disease.

Even though there was no evidence of the representativeness of study population, the authors believe that the results could be less affected by selection bias, which may arise from taking control from the outpatients in a hospital. Because the major reason of outpatients to visit this Prefectural Hospital was known to be for the diagnosis of any cancer, the patients from the Prefecture, as well as from the nearby Prefectures, having been once diagnosed in this Hospital, trended to visit other University Hospitals in the region for the treatment of the cancer. Moreover, it is a well-known fact that gathering information from patients prior to the diagnosis would be relatively free of bias due to selective recall. Any duplicate cases and controls were already sorted by their own hospital serial numbers, and removed from the study population by identification procedure using name, sex, birth year, residence, etc. Therefore there were absolutely no duplicates in both case and control group.

Age at menarche and natural menopause, menopausal status were nonsignificant variables, when their associations with breast cancer were assessed with an adjusted risk ratio for an age effect. The other variables on menstrual and reproductive behavior turned out to be significant in this population. Referring to recent information about the etiology of breast cancer^(3,14),

these findings were compatible with the hypothesis of the positive role of estrogen, as well as of a counterbalancing effect of progesterone in developing breast cancer. A protective effect of lactation against breast cancer was the same as the results from previous studies⁽¹⁵⁻¹⁷⁾. The influence of ovarian hormones, as well as hypothalamic or pituitary hormones, may have had an important role in this population.

The association of the number of siblings or birth order was not so prominent, while a positive family history of breast cancer among first relatives showed borderline significance. Although it is still unclear whether increased susceptibility is due to heritable factors and/or to common environmental exposure, an increased risk of the disease among those with a positive family history is a common finding around the world^(1,18-20).

Although drinking alcoholic beverages is one of the oldest and most widespread habits in the world, its relation to breast cancer is still not well understood. Results showed marked inconsistencies, because of difficulties in measuring and quantifying its consumption^(1,2). Unlike other papers⁽²¹⁻²⁴⁾, this hospital-based case-control analysis showed a protective effect of alcohol against breast cancer, independent of age, reproductive factors, lactation, and even smoking. Compared to Western women, female drinkers are not as common among Orientals, least of all heavy drinkers. Further analysis, including the effect of age at first drinking, will be needed to clarify this relationship.

The relation of smoking to the risk of breast cancer is another ambiguous point. The protective effect of smoking against breast cancer or no effect on the risk was reported through several epidemiologic studies^(21,25,26). Based on the finding of an unexpectedly low risk among smokers, it has been proposed that cigarette smoking may have an anti-estrogenic effect through direct action on the ovaries or by enhanced metabolism of steroid hormones in the liver⁽²⁷⁾. On the other hand, several cohort studies^(28,29), as well as case-control studies^(30,31), have found increased risk of breast cancer with smoking. A deleterious effect of smoking on breast cancer was found in our study. All aspects of smoking, for example, present smoking status, age at first smoking, and amount of smoking, showed significant dose-response gradients. If it is a fact that the hospital control is more likely to be a smoker than those in the general population, our results should be biased against the null, resulting in an underestimation of the true value. Unless we were missing other important factors which need to be controlled, it is evident that smoking should increase the risk of breast cancer. Mutagenic activity has been detected in nipple aspirates of human breast fluid⁽³²⁾. A direct effect of carcinogens on breast tissue seems to be plausible, but needs to be supported by further study.

Japanese women, like other Asians, have long been accustomed to a diet containing many vegetables. Even though overall dietary habits in Japan have been changing to the Western style, a preference for the traditional diet had not changed greatly among those in this population. Similar to other reports from various countries^(13,33-35), there was no evidence that a high fat diet affects the risk of breast cancer in this population. Meanwhile, green vegetables⁽³⁶⁾, as well as the Oriental staples, rice and bean curd (tofu), showed an apparent protective effect against breast cancer. A high intake of cabbage was positively associated with the risk, which is usually prepared in Western style, like salad.

In conclusion, several menstrual and reproductive factors were confirmed as major determinants of breast cancer in Japanese women, emphasizing the role of estrogen and progesterone on the risk in this population. In addition, significant associations with breastfeeding, smoking, drinking of alcohol, and some dietary habits suggest that further study under the specific hypothesis in a different population should be followed to confirm the different risk factors of breast cancer in Oriental people from those in the Western countries.

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