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A Large-scale, Hospital-based Case-Control Study of Risk Factors of Breast Cancer According to Menopausal Status

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We conducted a large-scale, hospital-based case-control study to evaluate differences and similarities in the risk factors of female breast cancer according to menopausal status. This study is based on a questionnaire survey on life style routinely obtained from outpatients who first visited the Aichi Cancer Center Hospital between January 1, 1988 and December 31, 1992. Among 36,944 outpatients, 1,186 women with breast cancer detected by histological examination were taken as the case group (607 premenopausal women and 445 postmenopausal women) and 23,163 women confirmed to be free of cancer were selected as the control group. New findings and reconfirmed factors of breast cancer were as follows. 1) The risk of at least one breast cancer history among subjects' first-degree relatives was relatively high among pre- as well as post-menopausal women. 2) A protective effect of physical activity against breast cancer was observed among both pre- and post-menopausal women. 3) Dietary control decreased the risk of premenopausal breast cancer. 4) Current smoking and drinking elevated the risk of breast cancer in premenopausal women. 5) Decreasing trends of breast cancer risk were associated with intake of bean curd, green-yellow vegetables, potato or sweet potato, chicken and ham or sausage in premenopausal women, while in postmenopausal women a risk reduction was associated with a more frequent intake of boiled, broiled and/or raw fish (sashimi). Further study will be needed to clarify the age group- and/or birth cohort-specific risk factors for breast cancer among the young generation in Japan.

Key words: Breast cancer — Risk factor — Menopause — Life style

Although the incidence rates of female breast cancer in most Asian countries are much lower than those in Western countries,[1,2] there has been a marked increase in recent years. It has been estimated that breast cancer will be the most common cancer among Japanese women by the year 2000.[3] The age distribution of breast cancer in Japanese women is entirely different from that of Western countries[4,5]; i.e., the age trend falls after menopause, even though the age-dependent elevation of risk in premenopausal women is somewhat similar. Since the drop in the age-specific incidence curve for breast cancer follows behind the average age of menopause, the etiologic factors for premenopausal breast cancer seem to be different from those for postmenopausal breast cancer. There has been considerable interest in the differences of risk factors between premenopausal breast cancer and postmenopausal breast cancer not only in Japan, but throughout the world. The present study was designed to elucidate the role of known and/or unknown risk factors of breast cancer, with particular emphasis on differences and similarities in the risk factors between pre- and post-menopausal cancers.

MATERIALS AND METHODS

Since 1988, self-administered questionnaires have been handed out to first-visit outpatients at Aichi Cancer Center Hospital (ACCH), Nagoya, Japan and information on life style has routinely been obtained. These questionnaires were collected before patients left the hospital after incomplete response items had been checked by a skilled interviewer. All the data were loaded into the computer system of the Division of Epidemiology, Aichi Cancer Center Research Institute.

Among all the first-visit outpatients between January 1988 and December 1992 (n=40,421), the questionnaire was administered to 37,882 patients. The remaining 2,539 patients were excluded because of lack of questionnaires, i.e., absence of the interviewer, age exclusion (younger than 18 years old), or a person other than the patient attended the consultation. Out of the 37,882 patients, 36,944 (97.5%) completed the questionnaire adequately.

The questionnaire includes items on occupation, medical history, height and weight (added since 1989), marital status, family history (parents and siblings), smoking and drinking habits, dietary habits, sleeping, physical exercise, bowel habits, and reproductive history in

females. The condition of these items prior to the present symptoms was inquired about and most information was collected before cancer and/or specific disease diagnosis was made.

The data collected from the questionnaire survey were linked to the hospital-based cancer registry files. Among 5,158 cancer patients detected by the hospital-based cancer registry, 1,186 women who were first diagnosed as having breast cancer confirmed by histological diagnosis, were taken as the case group and finally 1,052 cases were divided into two groups by menopausal status: 607 premenopausals and 445 postmenopausals. Four patients without information on menopausal status and 130 patients with no menstruation due to operation or other causes were excluded from further analyses. Among 31,786 non-cancer outpatients, 23,163 female patients were selected as the control group; women younger than 20 years old were excluded in the present study. Age distribution of cases and controls by menopausal status is shown in Table I.

Odds ratio (OR) and its 95% confidence interval (95%CI) for each exposure variable were estimated by using an unconditional logistic regression model adjusted for age and first-visit year. Utilizing the LOGISTIC

Table I. Age Distribution of Cases and Controls by Menopausal Status

Age	Menstruation						Total[a]	
	Yes		Natural menopause		Other[b]			
Cases								
–29	12	(2.0)	0	(0.0)	0	(0.0)	12	(1.0)
30–39	146	(24.1)	0	(0.0)	6	(4.6)	152	(12.8)
40–49	394	(64.9)	20	(4.5)	32	(24.6)	447	(37.7)
50–59	55	(9.1)	191	(42.9)	55	(42.3)	303	(25.6)
60–69	0	(0.0)	184	(41.4)	23	(17.7)	208	(17.5)
70–79	0	(0.0)	44	(9.9)	12	(9.2)	56	(4.7)
80+	0	(0.0)	6	(1.4)	2	(1.5)	8	(0.7)
Total	607	(100.0)	445	(100.0)	130	(100.0)	1,186	(100.0)
Controls								
–29	2,276	(15.1)	2	(0.0)	10	(0.6)	2,299	(9.9)
30–39	4,423	(29.3)	8	(0.1)	72	(4.0)	4,513	(19.5)
40–49	7,319	(48.5)	339	(5.5)	615	(34.5)	8,299	(35.8)
50–59	1,061	(7.0)	3,079	(49.5)	620	(34.8)	4,776	(20.6)
60–69	5	(0.0)	2,069	(33.3)	370	(20.8)	2,456	(10.6)
70–79	0	(0.0)	648	(10.4)	86	(4.8)	740	(3.2)
80+	0	(0.0)	70	(1.1)	10	(0.6)	80	(0.3)
Total	15,084	(100.0)	6,215	(100.0)	1,783	(100.0)	23,163	(100.0)

a) The total includes patients (4 cases and 81 controls) with unknown menstrual status.
b) No menstruation due to operation or other causes.

Table II. Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) for Breast Cancer by Menopausal Status among Patients with Family History of Breast Cancer

	Premenopausal			Postmenopausal		
	No. of cases/controls	OR	95%CI	No. of cases/controls	OR	95%CI
Breast cancer among first-degree relatives						
Mother or sister						
no	558/14088	1.00		398/5484	1.00	
yes	28/420	1.61*	1.09–2.39	23/166	2.03**	1.30–3.19
Mother						
no	587/14484	1.00		431/5976	1.00	
yes	14/266	1.44	0.83–2.48	6/63	1.45	0.62–3.37
Sister						
no	453/10186	1.00		348/4791	1.00	
yes	16/162	1.88*	1.11–3.18	17/112	2.21**	1.31–3.74

* $P<0.05$. ** $P<0.01$.

procedure from SAS[6] (SAS Institute), multivariate logistic regression was carried out using all the statistically significant variables from the first univariate analysis.

RESULTS

Occupation We investigated occupational distribution in cases and controls by menopausal status. In premenopausals, the occupation of housewife was given by 41% of the case group and 39% of the control group. In the case group the remaining occupations were office worker (19.1%), teacher and public officer (6.3%), part-timer (14.3%) and so on. The corresponding values in the control group were 19.0%, 6.0%, 16.7%, respectively. We also verified that the occupational distribution did not differ in the two groups of postmenopausals.

Family history As shown in Table II, an excess risk of breast cancer was found in patients who had at least one first-degree relative with a history of breast cancer. The risk was higher among postmenopausal women than among premenopausal women. The effect of family history on the risk of breast cancer was greater when a sister(s)

Table III. Age-adjusted and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of Anthropometric and Reproductive Variables for Breast Cancer by Menopausal Status

	Premenopausal			Postmenopausal		
	No. of cases/controls	OR	95%CI	No. of cases/controls	OR	95%CI
Height (cm)						
≤150	240/5082	1.00		256/3365	1.00	
151–158	251/6446	0.84	0.68–1.03	144/2324	1.01	0.81–1.28
159+	114/3357	0.89	0.69–1.15	44/480	1.54*	1.09–2.18
Weight (kg)						
≤48	290/6922	1.00		195/2909	1.00	
49–56	213/5284	0.91	0.75–1.11	121/2025	1.17	0.91–1.51
57+	104/2652	0.81	0.64–1.04	127/1246	2.05**	1.59–2.65
Body mass index[a]						
≤20.0	110/3638	1.00		38/1023	1.00	
20.1–26.4	308/7510	1.05	0.84–1.32	221/3476	1.77**	1.24–2.51
26.5+	32/530	1.44	0.96–2.18	61/474	3.60**	2.36–5.48
Marital status						
Married	532/12814	1.00		397/5712	1.00	
Single	58/1785	1.60**	1.18–2.16	12/181	0.95	0.52–1.72
Age at menarche (yr)						
≤13	347/8758	1.00		113/1451	1.00	
14–15	223/5438	0.82*	0.69–0.98	189/2715	0.87	0.68–1.11
16+	35/688	0.82	0.57–1.18	141/1979	0.84	0.65–1.09
Menstrual regularity						
regular	482/11012	1.00		348/4903	1.00	
irregular	124/3835	0.80*	0.65–0.97	88/1213	1.05	0.82–1.34
Delivery						
no	111/2936	1.00		54/624	1.00	
yes	496/11958	0.63**	0.50–0.79	391/5578	0.82	0.61–1.10
Age at first full-term pregnancy						
≤23	103/3139	1.00		120/1897	1.00	
24–26	215/5463	1.18	0.93–1.49	140/2082	1.09	0.84–1.40
27+	177/3330	1.63**	1.27–2.09	130/1574	1.34*	1.03–1.74
No. of birth						
0	111/2935	1.00		54/623	1.00	
1	75/1973	0.68*	0.50–0.92	63/762	0.98	0.67–1.43
2	300/7131	0.63**	0.49–0.79	184/2695	0.84	0.61–1.15
3+	121/2838	0.59**	0.45–0.78	144/2102	0.76	0.54–1.05
Average months of breast feeding						
Never	65/1091	1.00		22/391	1.00	
1–5	197/4201	0.84	0.63–1.12	61/933	1.16	0.70–1.91
6–11	107/3477	0.55**	0.40–0.76	89/1197	1.27	0.78–2.06
12+	127/3173	0.71*	0.52–0.96	218/3035	1.17	0.74–1.85

a) Body mass index was calculated by using the formula BMI=weight (kg)/height $(m)^2$.
* $P<0.05$. ** $P<0.01$.

was (were) positive than when the mother was positive, but the difference was not statistically significant.

Anthropometric and reproductive factors Age-adjusted ORs and 95% CIs of the anthropometric and reproductive variables for breast cancer by menopausal status are presented in Table III. A positive association with single status and older age at the first full-term pregnancy ($\geq$27 years) was observed among premenopausal women. An inverse association with older age at menarche ($\leq$13 years), irregular menstruation in the twenties, experience of delivery (yes), number of births and average months of breast feeding was also observed for premenopausal breast cancer. Positive associations with height, weight and body mass index (BMI) were especially marked in postmenopausal breast cancer. The younger the age at menarche and the older the age at the first full-term pregnancy, the higher was the risk of breast cancer. This finding was clearer among premenopausal women than among postmenopausal women.

Smoking and drinking habits, and physical activity In premenopausal women, current cigarette smoking showed a positive association with breast cancer (OR=1.35; 1.50 for those smoking 1–9 cigarettes per day and 1.31 for 10 or more). Passive exposure to environmental tobacco smoke from husband's smoking elevated the risk of breast cancer, particularly in postmenopausal breast cancer (Table IV). The risk of smokers who started smoking younger than 20 years old was a little higher than that of smokers who started smoking at older than 20 years of age both in premenopausal and postmenopausal women, but the differences were not statistically significant.

The OR of alcohol drinkers versus non-drinkers was 1.04 (95%CI=0.87–1.25) for premenopausal breast cancer, and a dose-response relationship was implied.

Physical exercise lowered the risk of breast cancer both in premenopausal women (OR=0.74) and postmenopausal women (OR=0.72).

Dietary habits The ORs of selected dietary habits for breast cancer by menopausal status are shown in Table V. The adjusted OR of dietary control (on a diet controlling salty food, fatty food or total calories) for premenopausal breast cancer was 0.73 (95%CI=0.57–0.94). Women under dietary control due to any disease/

Table IV. Age-adjusted and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of Habitual Smoking, Drinking and Physical Activity for Breast Cancer by Menopausal Status

	Premenopausal			Postmenopausal		
	No. of cases/controls	OR	95%CI	No. of cases/controls	OR	95%CI
Smoking						
nonsmokers	499/12535	1.00		399/5594	1.00	
smokers[a]	106/2341	1.35**	1.09–1.68	45/584	1.10	0.80–1.51
<10/day	32/676	1.50*	1.04–2.17	7/116	0.82	0.38–1.77
≥10/day	74/1653	1.31*	1.02–1.69	36/461	1.13	0.79–1.61
Passive smoking[b]						
non-smoker husband (no)	110/2916	1.00		82/1322	1.00	
smoker husband (yes)	222/5258	1.15	0.91–1.46	146/1780	1.39*	1.04–1.85
0–19/day	47/1625	0.81	0.57–1.15	65/685	1.55*	1.10–2.17
≥20/day	175/3633	1.30*	1.02–1.65	81/1095	1.28	0.92–1.77
Alcohol[c]						
nondrinker	413/10058	1.00		367/4987	1.00	
drinker	188/4683	1.04	0.87–1.25	68/1105	0.88	0.67–1.15
occasinonal	108/3241	0.89	0.72–1.10	46/715	0.92	0.67–1.26
≤1 go/day	52/1065	1.18	0.88–1.59	15/294	0.73	0.43–1.24
>1 go/day	28/353	2.03**	1.36–3.03	7/84	1.26	0.58–2.77
Sleeping time						
<6 h	35/830	1.00		46/699	1.00	
≥6 h	571/14034	1.03	0.73–1.46	394/5477	1.11	0.81–1.52
Physical activity (exercise for health)						
no	392/8717	1.00		257/3375	1.00	
occasional	161/4699	0.79*	0.65–0.95	126/1788	0.93	0.75–1.16
≥2 times/week	53/1448	0.74*	0.55–0.99	56/1007	0.72*	0.53–0.97

a) Number of cigarettes per day.
b) Nonsmoker without or with smoker husband: 167 cases in premenopausal and 171 cases in postmenopausal were excluded because of lack of information.
c) The unit of Japanese sake (1 go is equivalent to 180 ml and contains 28.8 ml of neat alcohol).
* $P<0.05$. ** $P<0.01$.

condition were excluded from this analysis. The levels of risk reduction of dietary control by salty food, fatty food or total calories did not differ from each other. Milk intake decreased the risk of postmenopausal breast cancer (OR=0.82, 95%CI=0.67–0.99). Rice intake for breakfast tended to lessen the risk of breast cancer and its risk reduction became distinct in women who consumed more than 3 bowls of rice per day.

Downward trends in the risk of breast cancer by consuming bean curd, green vegetables, carrot, potato or sweet potato, chicken, and ham or sausage were observed in premenopausal breast cancer, but were not clear in postmenopausal breast cancer. Intake of boiled or broiled fish and sashimi lowered the risk of breast cancer more in postmenopausal breast cancer than in premenopausal breast cancer (Table VI).

The adjusted ORs by multiple logistic regression analysis of 15 items which showed statistical significance in the univariate logistic model are shown in Table VII. The ORs were not very much different from those observed in univariate analyses.

DISCUSSION

This study should be free of patient response bias to the questionnaire because all data were collected from patients prior to their diagnosis. However, we can not escape from general issues on the selection bias of hospital controls. To determine the discrepancy between hospital outpatients and the general population we examined smoking prevalence, which may be a good indicator of general life style. Smoking prevalence in adult females in Japan is 13.3%, 17.9% in those 30–39 years old, 12.6% in those 40–49, 11.8% in those 50–59, 8.2% in those 60 or older (Japan Tobacco Company, 1992). The prevalences in our controls in the same age groups are 19.2%,

Table V. Age-adjusted and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of Dietary Habits for Breast Cancer by Menopausal Status

	Premenopausal			Postmenopausal		
	No. of cases/controls	OR	95%CI	No. of cases/controls	OR	95%CI
Saltiness						
dislike	233/5543	1.00		181/2460	1.00	
like	369/9266	0.97	0.82–1.15	250/3665	0.93	0.76–1.14
Fatty food						
dislike	306/7182	1.00		232/3424	1.00	
like	295/7601	0.95	0.80–1.11	203/2687	1.11	0.92–1.36
Type of breakfast						
bread, mixed skip	372/9262	1.00		218/2792	1.00	
rice	235/5622	0.91	0.77–1.08	224/3391	0.82	0.68–1.00
Number of rice bowls per day						
<3	229/5487	1.00		129/1813	1.00	
3+	238/5619	0.88	0.74–1.04	194/2520	0.88	0.72–1.07
Miso soup						
occasional, none	383/8615	1.00		276/3901	1.00	
daily	224/6268	1.16	0.98–1.37	167/2291	0.96	0.78–1.17
Milk						
occasional, none	364/8639	1.00		234/2933	1.00	
daily	241/6233	0.92	0.77–1.08	210/3237	0.82*	0.67–0.99
Raw vegetables						
≤3–4/wk	372/9348	1.00		260/3592	1.00	
daily	235/5546	1.00	0.85–1.19	185/2610	0.99	0.81–1.20
Fruit						
≤3–4/wk	357/8814	1.00		180/2565	1.00	
daily	247/6054	0.86	0.73–1.01	264/3610	1.02	0.84–1.24
Sweet dessert						
occasional, none	111/2682	1.00		90/1395	1.00	
daily	495/12189	0.96	0.78–1.19	353/4783	0.80	0.62–1.01
Dietary control[a]						
no	490/11772	1.00		254/3462	1.00	
yes	73/2015	0.73*	0.57–0.94	96/1506	0.93	0.73–1.20

a) On a diet controlling salty food, fatty food or total calories.
* $P<0.05$.

Table VI. Age-adjusted and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of 10 Food Items for Breast Cancer by Menopausal Status

	Premenopausal			Postmenopausal		
	No. of cases/controls	OR	95%CI	No. of cases/controls	OR	95%CI
Boiled or broiled fish, sashimi						
≤ 3/mo	121/3090	1.00		85/1003	1.00	
1–2/wk	289/7603	0.88	0.71–1.09	186/2656	0.82	0.63–1.07
≥ 3/wk	196/4171	0.98	0.78–1.24	168/2525	0.75*	0.57–0.98
Bean curd						
≤ 3/mo	86/2151	1.00		50/657	1.00	
1–2/wk	270/6291	0.93	0.72–1.19	151/2245	0.89	0.64–1.24
≥ 3/wk	250/6433	0.78	0.60–1.00	242/3284	0.96	0.70–1.31
Green vegetables						
≤ 2/wk	290/6728	1.00		195/2446	1.00	
3–4/wk	202/4873	0.88	0.74–1.06	113/2053	0.81	0.64–1.01
≥ 5/wk	114/3273	0.70**	0.56–0.87	115/1681	0.85	0.67–1.07
Carrot						
≤ 2/wk	349/7636	1.00		244/3170	1.00	
3–4/wk	190/5102	0.80*	0.67–0.96	114/1902	0.78*	0.62–0.98
≥ 5/wk	66/2133	0.66**	0.51–0.87	84/1097	1.03	0.79–1.33
Potato, sweet potato						
≤ 3/mo	113/2435	1.00		77/1097	1.00	
1–2/wk	300/6845	0.92	0.74–1.15	171/2590	0.95	0.72–1.26
≥ 3/wk	193/5578	0.70**	0.55–0.89	194/2497	1.11	0.85–1.46
Egg						
≤ 2/wk	175/3964	1.00		139/2059	1.00	
3–4/wk	231/5251	1.02	0.84–1.25	134/1904	1.05	0.82–1.34
≥ 5/wk	200/5670	0.82	0.67–1.01	169/2229	1.10	0.87–1.39
Chicken						
≤ 3/mo	164/3575	1.00		146/1777	1.00	
1–2/wk	329/8118	0.90	0.75–1.10	184/2850	0.78*	0.62–0.98
≥ 3/wk	111/3175	0.74*	0.58–0.94	113/1548	0.87	0.67–1.12
Beef						
≤ 3/mo	237/5738	1.00		230/3258	1.00	
1–2/wk	315/7412	1.05	0.89–1.25	168/2304	1.07	0.87–1.32
≥ 3/wk	54/1720	0.77	0.57–1.03	43/604	1.03	0.73–1.44
Pork						
≤ 3/mo	173/3905	1.00		220/2963	1.00	
1–2/wk	333/7993	1.00	0.83–1.22	166/2439	0.96	0.77–1.18
≥ 3/wk	98/2969	0.78	0.61–1.01	55/759	1.01	0.74–1.38
Ham, sausage						
≤ 3/mo	303/6194	1.00		279/4062	1.00	
1–2/wk	224/6039	0.87	0.72–1.04	102/1509	1.00	0.79–1.27
≥ 3/wk	79/2635	0.75*	0.58–0.97	62/600	1.50**	1.12–2.00

* $P<0.05$. ** $P<0.01$.

12.5%, 9.2%, 8.2%, respectively. From these figures, the features of smoking habits among the controls in the present study were not very much different from those of the general population. Furthermore, to compare general life-styles between hospital outpatients and the general population, we conducted a questionnaire study on members of the general population in Nagoya city by using the same questionnaire. We obtained the result that the average life-styles of outpatients who visited ACCH for the first time were not very different from those of community residents (unpublished data).

Among the 10% of randomly sampled non-cancer outpatients (n=2,997), 44.3% were free of disease. The remaining 55.7% were diagnosed as having benign tumor and/or non-neoplastic polyp (13.1%), mastitis (7.5%), digestive disease (4.1%), benign gynecological disease (4.1%) and so on. Another methodological study which used the same data set showed that the ORs based on a large number of controls gave more power and a steadier estimate than the use of matched controls,[7] therefore, we used all non-cancer individuals as the control group instead of matched controls.

Table VII. Multiple Logistic Regression Odds Ratios (ORs) of Selected Life-style Factors for Breast Cancer by Menopausal Status

	Premenopausal		Postmenopausal	
	OR	(95%CI)	OR	(95%CI)
BMI (>20 vs. ≤20)	1.13	(0.89–1.42)	1.99**	(1.40–2.82)
Age at menarche (>14 vs. ≤13)	0.72**	(0.59–0.88)	0.96	(0.73–1.25)
Delivery (yes vs. no)	0.76	(0.57–1.01)	0.72	(0.51–1.02)
Smoking (yes vs. no)	1.26	(0.97–1.64)	0.99	(0.66–1.48)
Physical activity (active vs. inactive)	0.64**	(0.48–0.84)	0.71*	(0.53–0.96)
Type of breakfast (rice vs. bread, mixed)	0.92	(0.75–1.13)	0.86	(0.68–1.08)
Milk (daily vs. occasional, none)	0.97	(0.79–1.20)	0.93	(0.73–1.19)
Fruit (daily vs. ≤3–4/wk)	0.95	(0.78–1.17)	1.05	(0.82–1.35)
Dietary control (yes vs. no)	0.78*	(0.61–0.99)	0.95	(0.75–1.20)
Bean curd (>3/wk vs. ≤3/wk)	0.81*	(0.65–0.99)	1.17	(0.92–1.49)
Green yellow vegetables (>3/wk vs. ≤3/wk)	1.02	(0.82–1.27)	0.86	(0.66–1.12)
Carrot (>3/wk vs. ≤3/wk)	0.91	(0.72–1.14)	0.82	(0.63–1.07)
Potato, sweet potato (>3/wk vs. ≤3/wk)	0.89	(0.71–1.11)	1.39*	(1.08–1.79)
Chicken (>1/wk vs. ≤1/wk)	1.04	(0.83–1.31)	0.78*	(0.60–1.00)
Ham, sausage (>1/wk vs. ≤1/wk)	0.88	(0.72–1.08)	1.12	(0.88–1.43)

* $P<0.05$. ** $P<0.01$.

There is clear evidence that a family history of breast cancer is associated with a 2–3 fold increased risk of breast cancer.[8–13] In this study the risk arising from at least one family history of breast cancer among first-degree relatives was elevated among pre- and post-menopausal women, and the effect was greater for women with an affected sister than for those with an affected mother. This finding may indicate a synergistic relationship between genetic factors and environmental factors; e.g., common genes and life style habits were influenced by the probands' mothers. The development of breast cancer is accepted to be the result of multiple genetic and environmental factors; however, its actual mechanism is not yet clearly known. Recent advances in molecular cancer genetics might clarify the important role of genetic factors, and further epidemiological studies and experimental research at the molecular level should provide information to aid the detection of high-risk individuals with a family history.

The association between obesity and breast cancer risk was first described by De Waard *et al.* in 1964[14] and has been uniformly reported from other countries.[15–17] In the present study, an increased risk of breast cancer was observed among postmenopausal women with greater height, greater weight, and greater BMI. Obesity may be mainly related to the risk of postmenopausal breast cancer. Accelerated conversion of androstenedione to estrone in the adipose tissue of obese women may result in an increased risk of breast cancer and the elevation of its conversion may be more prominent among postmenopausal women than among premenopausal women because of the secretion of estrogen from the ovary.[18]

In the present study, positive associations between reproductive variables and breast cancer risk were noted both in pre- and post-menopausal women, while the association with menstrual regularity in the twenties was opposite between premenopausal women and postmenopausal women. The statistically significant relationship of reproductive variables with premenopausal breast cancer was also consistent with findings in other studies conducted in Western countries.[19–21] These factors are probably related to hormonal changes affecting breast tissue proliferation during a full-term pregnancy.[22]

The association of breast cancer risk with lactation was more distinguished in premenopausal women than in postmenopausal women in this study. The protective effect of lactation was statistically significant among premenopausal women, while lactation increased the risk of postmenopausal breast cancer a little. The risk reduction of breast cancer by lactation in premenopausal women has been observed in several studies[23–27] including our previous study[24]; however, other epidemiologic studies failed to find a statistically significant level of negative relationship.[25–27]

In this study, active smoking elevated the risk of premenopausal breast cancer and passive smoking enhanced the risk of postmenopausal breast cancer. The effect of passive smoking in postmenopausal breast cancer might be the result of long-term accumulation of environmental tobacco smoke. MacMahon *et al.* demonstrated lower urinary estrogen levels in smokers than nonsmokers during the luteal phase of the menstrual cycle[28]; however, the role of estrogens in the etiology of breast cancer is still unclear, in either pre- or post-meno-

pausal breast cancer. Baron reviewed several studies on the relationship between smoking and breast cancer and concluded that there was no consensus.[29] Further evidence from epidemiologic and experimental studies must be provided to assess the role of smoking effects on estrogen metabolism.

Several epidemiologic studies have shown the positive association between alcohol consumption and breast cancer risk, as reviewed by Graham.[30] Kato *et al.* demonstrated that alcohol consumption elevated the risk of breast cancer in Japanese[31] as well as in Western women. In this study, a positive relationship between habitual drinking and breast cancer was found among premenopausal women, while it was not clear among postmenopausal women. At any rate, the drinking habit could account for a small attributable risk of postmenopausal breast cancer because the proportion of female drinkers in the older generation is very small in Japan and the amount of alcohol consumption by female drinkers is much lower in Japan than that in Western countries.

A negative relationship between physical activity and breast cancer was observed among both pre- and postmenopausal women in this present study. A risk reduction in breast cancer among ballet dancers and college athletes was observed in previous studies.[32, 33] Physical activity may protect against breast cancer by its action on the ovulatory cycle or by elevation of natural killer cell function.

The OR of breast cancer among women under dietary control was 0.73 in premenopausal women and 0.93 in postmenopausal women. Perceived change in dietary habits, such as fat intake control and total calories control, might modulate the risk of breast cancer. A risk reduction compatible with several previous studies,[12, 34] was associated with a more frequent intake of green-yellow vegetables. For daily intake of milk, significant differences in the proportional frequencies between cases and controls were observed among postmenopausal women. Van't Veer *et al.* reported no significant relationship between consumption of milk and breast cancer, whereas a high consumption of fermented milk products protected against breast cancer in the same study.[35] We have to be cautious in interpreting the findings obtained from these epidemiological studies in Western countries because of the great differences in the amount of dairy products intake between Japanese and Western people.

Since breast cancer has been most common in Western countries, its etiological factors have been reviewed by many researchers.[22, 36–39] It is important to elucidate the risk factors for breast cancer in Oriental countries, including Japan, where the incidence of breast cancer is running at lower levels but is gradually increasing. Furthermore, age-specific incidence curves of breast cancer in Japanese women were characteristic; i.e., only the postmenopausal incidence is much lower than that in Western women. The present study focused on the particular differences in risk factors for breast cancer between premenopausal women and postmenopausal women and provided evidence that the known risk factors of breast cacner seen in Western countries also affect low-risk populations and that the risk factors of breast cancer in premenopausal women are very different from those in postmenopausal women in Japan.

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