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Subsite (cervix/endometrium)-specific Risk and Protective Factors in Uterus Cancer

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In Japan the incidence of cervical cancer has been high, but has recently been decreasing gradually, while the incidence of endometrial cancer is running at lower levels but is gradually increasing. To clarify the common and/or specific risk and/or protective factors of cervical cancer(CC) in contrast with endometrial cancer (EC), a comparative case-control study was conducted at the Aichi Cancer Center Hospital, Japan. In total, 556 CC cases and 145 EC cases were included and 26,751 women, confirmed as free of cancer, were chosen as the common control group. Odds ratio 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. Habitual smoking and experience of pregnancy increased the risk of CC, while decreasing the risk of EC. Greater body mass index (>20), daily intake of fruit and more frequent intake of boiled or broiled fish (>1–2 times/week) decreased the risk of CC, whereas they increased the risk of EC. Daily intake of milk decreased the risk of CC. The results obtained from this study suggest that several EC-increasing risk factors are in fact CC-decreasing determinants. The observed risk reduction in both CC and EC by physical exercise and dietary control for health is noteworthy from the public health standpoint and warrants further investigation.

Key words: Uterus cancer — Subsite — Case-control study — Risk factors

The handbook "Cancer Incidence in Five Continents" reported that the incidence of cervical cancer (hereafter referred to as CC) is about twice as high in Japan as in Europe and North America.[1)] In contrast, the incidence rate ratio of endometrial cancer (hereafter referred to as EC) vs. CC in Asia including Japan (Japan Osaka, 1983–1987 rate ratio 0.20; average annual incidence rate 2.7 vs. 13.2 per 100,000) is extremely low compared with that of Western countries including the United States (USA White, 1983–1987 rate ratio 2.63; average annual incidence rate 19.2 vs. 7.3 per 100,000). There has been considerable interest in the differences of risk factors between CC and EC in Japan.

Because of the low frequency of EC, there have been rather few analytical epidemiological studies in Japan, although its etiological factors have been reviewed by many researchers in western countries. Nevertheless, it is important to elucidate the risk factors for EC in Oriental countries, including Japan, where the incidence of EC is running at lower levels, but is gradually increasing.

The presence of certain types of human papillomaviruses (HPV) is one of the major risk factors in the development of CC. However, factors other than HPV infections may also play important roles in CC. Risk factors other than HPV appear to exist, especially in HPV-negative women, and HPV may not be the only factor that determines the development of CC in China and Taiwan.[2)]

To elucidate the role of known and/or unknown risks as well as protective factors in uterus cancer, we conducted a comparative case-control study of subsites of uterus cancer, i.e., CC ,which has been dominant, but has recently been decreasing gradually, and EC, in the low-risk Japanese population. In particular, we focused on the differences and similarities between CC and EC.

MATERIALS AND METHODS

Since 1988, a self-administered questionnaire survey has been completed by first-visit outpatients at the Aichi Cancer Center Hospital (ACCH), Nagoya, Japan. All questionnaire sheets have been collected on the first-visit day after checking for incomplete responses by a trained interviewer. All the data have been loaded into the computer system of the Aichi Cancer Center Research Institute. Details of the questionnaire and data collection procedures have been described elsewhere.[3–5)]

Of all the first-visit outpatients, totaling 47,895 between January 1988 and December 1993, the questionnaire was administered to 44,502 patients. The remaining 3,393 patients were excluded due to interviewer absence, age exclusion (younger than 18 years old), or visit only

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Table I. Age Distribution of Cases and Controls

Age group	Number of cases (%)		Number of controls (%)
	Cervix	Endometrium	
20–29	22 (4.0)	1 (0.7)	2545 (9.5)
30–39	106 (19.1)	7 (4.8)	5226 (19.5)
40–49	166 (29.9)	26 (17.9)	9601 (35.9)
50–59	110 (19.8)	60 (41.4)	5595 (20.9)
60–69	82 (14.7)	40 (27.6)	2858 (10.7)
70–79	57 (10.3)	7 (4.8)	844 (3.2)
80+	13 (2.3)	4 (2.8)	82 (0.3)
Total	556(100.0)	145(100.0)	26751(100.0)
Average age±SD	50.9±14.0	55.3±10.2	45.8±12.2

for consultation. Of the 44,502 patients, 43,759 (98.3%) 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 pattern, physical exercise, bowel habits and reproductive history in females. Frequency of intake of certain foods is classified into 5 categories: every day; 3–4 times per week; 1–2 times per week; 1–3 times per month, never. We did not include questions on socioeconomic status or education in our questionnaire, because Japanese are generally reluctant to answer such questions. It is generally acknowledged that the majority of Japanese consider themselves middle-class. The answers on the questionnaire refer to conditions prior to the symptoms with which the outpatients presented, and all information was collected before diagnoses were made.

The data collected were linked with the hospital-based cancer registry files. Among 9,172 cancer patients in the hospital-based cancer registry, 556 women and 145 women first diagnosed as having CC and EC, respectively, by histological diagnosis were taken as the case group. Controls were 26,751 female first-visit outpatients aged 20 years or older who had never had a diagnosis of cancer. Table I lists the 26,751 controls, 556 CCs and 145 ECs by age group.

The distribution of continuous variables was examined among cases and controls and divided into two or three categories. The body mass index (BMI = body weight/height^2) was categorized into three groups; thin($\leqq$20), moderate(20–26.5) and fat($\geqq$26.5), respectively, though the BMI at around 20 years of age was recategorized into $\leqq$20, 20–24.0 and $\geqq$24.0, respectively. 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. The *P* value for trend corresponded to the estimate of the slope derived from the logistic model in the case that the integers, 1 to n, were assigned to the ordered n levels of each factor. Utilizing the LOGISTIC procedure provided by SAS (SAS Institute), multivariate logistic regression analysis was carried out for all the statistically significant variables from the prior univariate analysis.

RESULTS

The age- and first-visit year-adjusted ORs and 95% CIs of the reproductive variables for CC and EC are presented in Table II. Unmarried status and older age ($\geq$24 years) at first full-term pregnancy showed a statistically significant negative association with CC, but an inverse association with EC. The negative relationship between EC and pregnancy or number of births was statistically significant. Irregular menstruation in the twenties lowered the ORs in both CC and EC, but was not statistically significant. Table III indicates that taller women were at higher risk of CC than shorter women, while heavier women were at higher risk of EC than lighter women. When BMI was used, a negative association with CC and a positive association with EC were observed. However, greater BMI at around 20 years of age decreased the risk not only of CC, but also of EC.

The ORs of current cigarette smoking were 2.19 (95% CI: 1.78–2.69) for CC and 0.69 (95%CI: 0.37–1.27) for EC (Table IV). Passive exposure to environmental tobacco smoke from husband's smoking elevated the risk of CC, although it did not affect the risk of EC. The OR for alcohol drinkers versus nondrinkers for CC was 1.21 (95%CI: 0.99–1.47), whereas an inverse trend was seen for EC. When the nonsmoker and nondrinker group was taken as the reference, the ORs for nonsmoker and current drinker, current smoker and nondrinker, current smoker and current drinker for CC were 1.04 (95%CI: 0.82–1.33), 2.11 (95%CI: 1.57–2.84) and 2.47 (95%CI: 1.83–3.34), respectively. Their ORs for EC were 1.13 (95%CI: 0.73–1.74), 0.95 (95%CI: 0.44–2.06), 0.53 (95%CI: 0.17–1.68), respectively, and the joint effect of

Table II. Age- and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of Reproductive Variables for Cervical and Endometrial Cancer

		Cervical cancer			Endometrial cancer		
		No. of cases/controls	OR	(95%CI)	No. of cases/controls	OR	(95%CI)
Age at menarche (yr)	≦13	211/12836	1.00		43/12836	1.00	
	14–15	235/10339	1.12	(0.92–1.36)	67/10339	1.31	(0.88–1.94)
	≧16	105/3474	1.10	(0.84–1.44)	33/3474	1.11	(0.67–1.84)
Menstruation aged 20's	regular	440/20139	1.00		116/20139	1.00	
	irregular	35/2475	0.72	(0.51–1.03)	10/2475	0.84	(0.44–1.62)
Marital status	married	500/23591	1.00		132/23591	1.00	
	single	18/2489	0.52**	(0.32–0.84)	8/2489	1.25	(0.60–2.59)
Pregnancy	no	50/3695	1.00		26/3695	1.00	
	yes	506/23049	1.21	(0.90–1.62)	119/23049	0.47**	(0.31–0.73)
Age at first full-term pregnancy	≦23	181/6375	1.00		24/6375	1.00	
	24–26	181/9526	0.73**	(0.59–0.90)	58/9526	1.97**	(1.22–3.19)
	≧27	117/6182	0.72**	(0.57–0.91)	34/6182	1.74*	(1.03–2.95)
No. of births	0	73/4603	1.00		29/4603	1.00	
	1	78/3512	1.14	(0.83–1.58)	19/3512	0.63	(0.35–1.14)
	2	238/12389	0.97	(0.74–1.26)	64/12389	0.62*	(0.40–0.96)
	≧3	165/6204	1.11	(083–1.48)	33/6204	0.41**	(0.25–0.69)
Breast feeding	no	65/2826	1.00		9/2826	1.00	
	yes	438/20174	0.84	(0.65–1.10)	110/20174	1.38	(0.70–2.73)

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

Table III. Age- and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of Anthropometric Variables for Cervical and Endometrial Cancer

		Cervical cancer			Endometrial cancer		
		No. of cases/controls	OR	(95%CI)	No. of cases/controls	OR	(95%CI)
Height (cm)	≦150	132/5455	1.00		38/5455	1.00	
	151–158	209/11513	0.97	(0.77–1.22)	65/11513	1.37	(0.89–2.10)
	≧159	103/5074	1.29	(0.97–1.72)	17/5074	1.17	(0.63–2.17)
Weight (kg)	≦48	156/7027	1.00		31/7027	1.00	
	49–56	176/9719	0.83	(0.67–1.03)	43/9719	1.09	(0.68–1.73)
	≧57	111/5263	0.93	(0.73–1.19)	44/5263	1.94**	(1.22–3.08)
BMI[a)]	≦20.0	135/5950	1.00		21/5950	1.00	
	20.1–26.4	275/14613	0.72**	(0.58–0.89)	76/14613	1.18	(0.73–1.92)
	≧26.5	32/1397	0.79	(0.54–1.18)	21/1397	2.86**	(1.55–5.27)
BMI[b)]	≦20	208/9645	1.00		51/9645	1.00	
	20.1–23.9	193/10701	0.77*	(0.63–0.94)	59/10701	0.88	(0.60–1.29)
	≧24	37/1466	0.90	(0.63–1.30)	8/1466	0.58	(0.27–1.25)

a) Body mass index was calculated by using the formula, BMI = weight (kg)/height $(m)^2$.
b) Calculated by weight at around 20 years of age.
* $P<0.05$, ** $P<0.01$.

habitual drinking and habitual smoking on CC or EC was not remarkable. Physical exercise for health lowered the risk of both CC (OR = 0.56, 95%CI: 0.44–0.72) and EC (OR = 0.60, 95%CI: 0.38–0.93).

The age- and first-visit year-adjusted ORs of selected dietary habits for CC and EC are compiled in Table V. The ORs for CC by daily intake of milk, raw vegetables and fruit were 0.71 (95%CI: 0.60–0.85), 0.88 (95%CI: 0.74–1.04) and 0.70 (95%CI: 0.59–0.83), respectively, whereas they were 1.17 (95%CI: 0.84–1.63), 1.54 (95% CI: 1.11–2.13), and 1.97 (95%CI: 1.37–2.82) for EC, respectively. The OR of rice intake for breakfast for EC was 1.47 (95%CI: 1.05–2.06). The ORs for CC by dietary control for health (on a diet controlling salty food, fatty

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

	Cervical cancer			Endometrial cancer		
	No. of cases/controls	OR	(95%CI)	No. of cases/controls	OR	(95%CI)
Smoking						
nonsmoker	431/23067	1.00		134/23067	1.00	
smoker	125/3658	2.19**	(1.78–2.69)	11/3658	0.69	(0.37–1.27)
<10/day[a)]	19/969	1.32	(0.83–2.11)	2/969	0.52	(0.13–2.12)
≧10/day	106/2663	2.50**	(2.01–3.11)	9/2663	0.75	(0.38–1.49)
Passive smoking[b)]						
non-smoker husband	205/10873	1.00		71/10873	1.00	
smoker husband	210/10159	1.30**	(1.07–1.59)	54/10159	1.09	(0.76–1.57)
<20/day	67/3962	1.00	(0.76–1.33)	22/3962	1.02	(0.63–1.65)
≧20/day	142/6103	1.55**	(1.24–1.94)	31/6103	1.14	(0.73–1.76)
Alcohol[c)]						
nondrinker	392/19037	1.00		112/19037	1.00	
drinker	152/7324	1.21	(0.99–1.47)	32/7324	1.02	(0.68–1.53)
occasional	96/4991	1.17	(0.93–1.48)	24/4991	1.15	(0.73–1.80)
≦1 *go*/day	36/1732	1.14	(0.81–1.62)	6/1732	0.74	(0.32–1.69)
>1 *go*/day	19/577	2.00**	(1.25–3.20)	1/577	0.44	(0.06–3.17)
Sleeping time						
<6 h	55/2027	1.00		8/2027	1.00	
≧6 h	499/24639	0.88	(0.66–1.16)	136/24639	1.92	(0.94–3.95)
Physical activity (exercise for health)						
no	367/15160	1.00		98/15160	1.00	
occasional	106/5903	0.74**	(0.59–0.92)	22/5903	0.56*	(0.35–0.89)
≧3–4 times/week	82/5617	0.56**	(0.44–0.72)	25/5617	0.60*	(0.38–0.93)

a) Number of cigarettes per day.
b) Nonsmoker without or with smoker husband: 16 cases in cervical cancer and 9 cases in endometrial cancer 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 net alcohol).
* $P<0.05$, ** $P<0.01$.

food and/or total calories) were 0.57 (95%CI: 0.45–0.74) and 0.67 (95%CI: 0.42–1.05) for EC. The levels of risk reduction by dietary control on salty food, fatty food or total calories did not differ from each other.

Table VI gives age- and first-visit year-adjusted ORs of selected food items for CC and EC. Downward trends in the risk of CC for consumers of boiled or broiled fish, bean curd, green vegetables, carrot, pumpkin and egg were found, but were not clear for EC. The decreasing trends in the risk of CC with increasing intake of these foods were statistically significant ($P<0.01$).

The adjusted ORs obtained by multiple logistic regression analysis of 16 items which showed statistical significance in the univariate analysis are shown in Table VII. The ORs were not much different from those observed in univariate analyses. Four items (physical exercise, daily intake of milk, dietary control and frequent intake of fish) still lowered ORs and smoking habit elevated ORs for CC, even after consideration of other factors. The ORs for older age at first full-term pregnancy, greater BMI and rice intake for breakfast from multiple logistic regression analysis were elevated in EC in a statistically significant manner.

DISCUSSION

A methodological issue of the present study was the possible bias caused by using hospital-based controls. Discrepant characteristics between the general population and hospital-based controls are sometimes apparent.

In Japan, outpatients, in general, visit hospitals when they have symptoms, and the number of outpatients who visit general clinics has been decreasing while the number of those who visit hospitals has been increasing in the past 10 to 15 years.[6)] This situation is very different from that in other countries, where people visit local general clinics first, and then hospitals which function as secondary facilities for further medical treatment. Since most people in Japan make first contact with the health system through a hospital, the majority of the first-visit outpatients were found to be disease-free after a series of general medical checks, especially cancer screening. Most

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

	Cervical cancer			Endometrial cancer		
	No. of cases/controls	OR	(95%CI)	No. of cases/controls	OR	(95%CI)
Saltiness						
dislike	199/10409	1.00		54/10409	1.00	
like	355/16298	1.18	(0.99–1.40)	90/16298	1.13	(0.81–1.59)
Fatty food						
dislike	300/13695	1.00		72/13695	1.00	
like	254/12973	0.95	(0.80–1.13)	72/12973	1.20	(0.86–1.66)
Type of breakfast						
bread, mixed and skip	295/15296	1.00		60/15296	1.00	
rice	259/11412	1.00	(0.85–1.19)	85/11412	1.47*	(1.05–2.06)
Milk						
occasional, none	335/14494	1.00		67/14494	1.00	
daily	217/12185	0.71**	(0.60–0.85)	77/12185	1.17	(0.84–1.63)
Raw vegetables						
≦3–4/wk	346/16244	1.00		69/16244	1.00	
daily	207/10422	0.88	(0.74–1.04)	76/10422	1.54*	(1.11–2.13)
Fruit						
≦3–4/wk	318/14319	1.00		44/14319	1.00	
daily	234/12358	0.70**	(0.59–0.83)	101/12358	1.97**	(1.37–2.82)
Dietary control[a]						
no	431/19029	1.00		100/19029	1.00	
yes	76/4777	0.57**	(0.45–0.74)	24/4777	0.67	(0.42–1.05)

a) On a diet controlling salty food, fatty food or total calories.
* $P<0.05$, ** $P<0.01$.

new outpatients visited the ACCH independently, rather than through doctors' referrals. Therefore, patients with incident cancer comprised only 19 percent of all new outpatients. Sixty percent of the non-cancer group visited the hospital three times or less. Among the randomly sampled non-cancer outpatients ($n=1,000$) in 1988–1989, only 34% were found to have some specific disease. The most common diseases in that group were polyps, mastopathy and fibroadenoma.[7] We are, therefore, at an advantage at ACCH, in having non-cancer outpatients as controls, most of whom were not hospitalized and were disease-free.

This study would be free of patient response bias to the questionnaire, because all data were collected prior to diagnosis; however, we can not escape from the general issues of selection bias in outpatient 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 aged 40–49, 11.8% in those aged 50–59, and 8.2% in those aged 60 or older (Japan Tobacco Company, 1992). The prevalences in our controls in the same age groups are 12.2%, 17.4%, 11.9%, 8.0%, and 6.6%, 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, although a slightly lower rate was noted in the older age group. Furthermore, from our collaborative study on the general population in Nagoya City by using the common questionnaire, the average life-style of first-visit outpatients who visited the ACCH (located in Nagoya City) was not very different from those of community residents (unpublished results). There were no differences between outpatients and the community sample in terms of age at first birth, number of births, nulligravidity and age at menarche. Another methodological study applying 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[8]; therefore, we used all non-cancer individuals as controls instead of matched ones.

Biological plausibility has been proven by abundant experimental data demonstrating the oncogenic potential of HPV and epidemiological studies have shown that the association of HPV with CC is strong and independent of other risk factors. However, it remains important to examine the role of other putative CC risk factors in the development of this disease.

Table VI. Age- and First-visit Year-adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95%CI) of 9 Food Items for Cervical and Endometrial Cancer

	Cervical cancer			Endometrial cancer		
	No. of cases/controls	OR	(95%CI)	No. of cases/controls	OR	(95%CI)
Boiled or broiled fish, sashimi						
≦3/mo	132/5140	1.00		22/5140	1.00	
1–2/wk	274/13055	0.79*	(0.64–0.97)	66/13055	1.15	(0.71–1.87)
≧3/wk	147/8491	0.56**	(0.44–0.72)	57/8491	1.24	(0.75–2.03)
Bean curd						
≦3/mo	90/3591	1.00		22/3591	1.00	
1–2/wk	241/10829	0.84	(0.66–1.08)	54/10829	0.77	(0.47–1.27)
≧3/wk	223/12280	0.63**	(0.49–0.81)	69/12280	0.76	(0.47–1.23)
Green vegetables						
≦2/wk	288/11532	1.00		54/11532	1.00	
3–4/wk	164/8800	0.71**	(0.59–0.87)	51/8800	1.17	(0.80–1.72)
≧5/wk	99/6361	0.56**	(0.45–0.71)	39/6361	1.12	(0.74–1.70)
Carrot						
≦2/wk	329/13481	1.00		82/13481	1.00	
3–4/wk	151/8878	0.70**	(0.58–0.85)	36/8878	0.68	(0.46–1.01)
≧5/wk	71/4307	0.65**	(0.50–0.84)	27/4307	0.94	(0.60–1.45)
Pumpkin						
≦3/mo	305/13886	1.00		74/13886	1.00	
1–2/wk	180/9339	0.82*	(0.68–0.99)	52/9339	0.91	(0.63–1.30)
≧3/wk	67/3458	0.73*	(0.55–0.95)	19/3458	0.72	(0.43–1.20)
Egg						
≦2/wk	196/7808	1.00		48/7808	1.00	
3–4/wk	187/9087	0.89	(0.73–1.09)	52/9087	1.10	(0.74–1.63)
≧5/wk	170/9825	0.72**	(0.59–0.89)	45/9825	0.82	(0.55–1.24)
Chicken						
≦3/mo	172/6911	1.00		39/6911	1.00	
1–2/wk	249/13818	0.78*	(0.64–0.95)	72/13818	1.07	(0.72–1.59)
≧3/wk	132/5953	0.89	(0.70–1.11)	34/5953	1.02	(0.64–1.62)
Beef						
≦3/mo	262/11477	1.00		65/11477	1.00	
1–2/wk	235/12313	0.95	(0.79–1.13)	65/12313	1.18	(0.83–1.67)
≧3/wk	53/2886	0.89	(0.66–1.20)	14/2886	1.04	(0.58–1.87)
Pork						
≦3/mo	218/8859	1.00		58/8859	1.00	
1–2/wk	261/13187	0.97	(0.81–1.17)	71/13187	1.19	(0.83–1.70)
≧3/wk	73/4623	0.79	(0.60–1.04)	16/4623	0.81	(0.46–1.42)

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

In this study these observations in relation to reproductive factors were essentially consistent with the results obtained in many other studies.[9–12] Therefore, we focused on finding modifiable protective factors against uterus cancer in contrast to the two specific uterine sites.

The present study provided clear evidence that higher odds ratios for EC were related to greater BMI adjusted for other factors in the multivariate model (Table VII). The relationship between obesity and risk of EC has been uniformly reported from other countries[9, 10, 13–15] and obesity is associated with an increased extraglandular conversion of androgen to estrogen.[16–18] Also, excess body weight is associated with a diminished capacity of serum sex-hormone-binding globulin and an elevated percentage of serum estradiol in the free state,[18] which may be related to the risk enhancement of EC.

Numerous epidemiological studies have shown a positive association between smoking and CC.[19] Simons *et al.* reported a relation between smoking and the proportions of DNA adducts in cervical epithelium, and provided direct biochemical evidence of potentially carcinogenic agents.[20] The result obtained from the present study in regard to the relation between CC and habitual smoking is entirely consistent with others (Table IV). Conversely, active smoking was shown not to be associated with the risk of EC in this study. It is known that the high degree

Table VII. Multiple Logistic Regression Odds Ratios (ORs) of 16 Selected Life-style Factors for Uterus Cancer by Subsite

	Cervix		Endometrium	
	OR	(95%CI)	OR	(95%CI)
Age at first full-term gregnancy (≥24 vs. <24)	0.89	(0.72–1.12)	1.90*	(1.13–3.19)
No. of births (≥3 vs. 0–2)	1.04	(0.82–1.31)	0.79	(0.50–1.27)
BMI (≧26.5 vs. <26.4)	1.04	(0.70–1.53)	3.01**	(1.79–5.06)
Smoking (yes vs. no)	1.76**	(1.34–2.32)	1.02	(0.48–2.14)
Physical activity (active vs. inactive)	0.71*	(0.53–0.95)	0.63	(0.34–1.11)
Type of breakfast (rice vs. bread, mixed)	1.16	(0.94–1.44)	1.67*	(1.08–2.57)
Milk (daily vs. occasional, none)	0.77*	(0.62–0.96)	1.04	(0.68–1.60)
Raw vegetables (daily vs. occasional, none)	1.19	(0.95–1.50)	1.53	(0.98–2.38)
Fruit (daily vs. occasional, none)	0.84	(0.67–1.06)	1.50	(0.94–2.41)
Dietary control (yes vs. no)	0.62**	(0.48–0.80)	0.71	(0.45–1.12)
Fish (>1–2/wk vs. ≤3/mo)	0.71**	(0.56–0.91)	1.46	(0.78–2.71)
Bean curd (≥3/wk vs. <1–2/wk)	0.90	(0.73–1.13)	0.80	(0.52–1.23)
Green vegetables (≥3/wk vs. <1–2/wk)	1.02	(0.80–1.29)	1.28	(0.79–2.08)
Carrot (≥3/wk vs. <1–2/wk)	0.90	(0.71–1.14)	0.75	(0.47–1.19)
Pumpkin (>1–2/wk vs. ≤3/mo)	0.97	(0.78–1.21)	0.93	(0.61–1.44)
Egg (≥3/wk vs. <1–2/wk)	0.96	(0.76–1.20)	0.85	(0.54–1.34)

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

of proliferation in endometrial tissue is due to continuous stimulation by estrogen. Since cigarette smoking affects estrogen production or metabolism, leading to reduced estrogenic stimulation,[21,22] female smokers may experience lower EC incidence during their life.

High alcohol intake may modify gonadotropin and prolactin levels, and cause anovulation. Alteration of hormone and sex hormone-binding globulin levels may also modify the risk of EC. However, epidemiological data on the relation between alcohol consumption and risk of EC are scant and controversial.[23–26] The present study showed a decreased risk of EC (Table IV), while no relation emerged from the analysis of the combined effect of habitual smoking and drinking. On the other hand, those who consumed more than 1 *go* of Japanese sake per day had an increased risk of CC. At any rate, the drinking habit could account for a small etiologic fraction of uterus cancer because the proportion of female drinkers is very small and alcohol consumption by females in Japan is much lower than that in Western countries.

It was remarkable that the subjects who took more frequent physical exercise for health had a lower lifetime occurrence of cervical and endometrial cancer than those who took less (Table IV). A reduced risk of reproductive system cancer was reported among former college athletes.[27] An adequate level of physical exercise may be protective against uterus cancer by its action on the ovulatory cycle or by elevation of natural killer cell function. Dietary control for health may lower the risk of both CC and EC. Perceived changes in dietary habits, such as fat intake and total calorie control, might also modulate the risk of uterus cancer.

Dietary factors have been claimed to play an important role in the etiology of uterus cancer. The present study showed that daily intake of raw vegetables and fruit, which may be one of the indicators of western life style in Japan, was positively associated with the risk for EC. In this study intake of rice for breakfast elevated the risk of EC, which was contradictory to our original hypothesis that the risk of EC may be enhanced by western life style and be reduced by Japanese traditional dietary habits (including intake of rice for breakfast). Further studies are required to confirm the relation between rice intake for breakfast and EC in Japanese women in terms of the possible biological effect of rice, *per se*, and/or other possible confounding factors.

Conversely, the decreased OR for CC by frequent intake of green-yellow vegetables and fruit suggested that certain ingredients, i.e., vitamins and trace minerals, might play a role in the protective effect against CC. Dietary studies on beta-carotene and CC have yielded inconsistent results, though serologic studies were slightly more consistent.[28–31] Our results show an inverse association between CC and dietary consumption of foods rich in beta-carotene. However, this must be interpreted with considerable caution, not only because all dietary survey methods present problems with respect to reliability and validity, but also because of the limited number of dietary variables collected in this study. Further study will be needed to clarify how vegetable sources of beta-carotene relate to the established risk factors for CC,

such as sexual history. We observed risk decrements in CC for daily intake of milk and frequent intake of boiled, broiled or raw fish, after adjusting for other factors. These effects might be explained by reference to any of a number of biochemical properties of these foods. The question of the role of diet in the etiology of CC seems as yet to be unresolved.

In the present study, we focused on the differences in risk and protective factors between CC and EC, and suggested that the risk and/or protective factors for uterus cancer varied with subsite to a considerable degree. In most studies from Western countries, nulliparity, older age at first pregnancy and obesity have been confirmed as risk factors for developing EC. The results provided evidence that known risk factors of EC seen in other countries also affect Japanese women. Although relatively little analytical epidemiologic information has been published on the relation between diet and EC, the present study on Japanese women has demonstrated that rice intake for breakfast and daily intake of raw vegetables and fruit are associated with EC in a statistically significant manner. These dietary factors might be peculiar risk factors of EC in Japan, and seem to warrant more detailed investigation.

The results derived from the present study provide a clue to a strategy for prevention of uterus cancer. It is important to quit smoking for CC prevention. Moreover, our analyses suggested that there are some modifiable factors among dietary habits. The observed risk reduction in uterus cancer by physical exercise and dietary control for health is noteworthy from the public health standpoint.

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