

## Lactation and Risk of Endometrial Cancer in Japan: A Case-Control Study

CHIKAKO OKAMURA, YOSHITAKA TSUBONO,<sup>1</sup> KIYOSHI ITO, HITOSHI NIIKURA,  
TADAO TAKANO, SATORU NAGASE, KOHSUKE YOSHINAGA, YUKIHIRO TERADA,  
TAKASHI MURAKAMI, SHINJI SATO,<sup>2</sup> DAISUKE AOKI,<sup>3</sup> TOSHIKO JOBBO,<sup>4</sup>  
KUNIHIRO OKAMURA and NOBUO YAEGASHI

*Department of Obstetrics and Gynecology, Tohoku University Graduate School  
of Medicine, Sendai, Japan,*

<sup>1</sup>*Tohoku University School of Public Policy, Sendai, Japan,*

<sup>2</sup>*SS Ladies Clinic, Sendai, Japan,*

<sup>3</sup>*Department of Obstetrics and Gynecology, Keio University School of Medicine,  
Tokyo, Japan, and*

<sup>4</sup>*Department of Obstetrics and Gynecology, Kitasato University School of  
Medicine, Kanagawa, Japan*

OKAMURA, C., TSUBONO, Y., ITO, K., NIIKURA, H., TAKANO, T., NAGASE, S., YOSHINAGA, K.,  
TERADA, Y., MURAKAMI, T., SATO, S., AOKI, D., JOBBO, T., OKAMURA, K. and YAEGASHI, N.  
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Exp. Med., 2006, **208** (2), 109-115 — The incidence of endometrial cancer is rapidly  
increasing in Japan. Although the risk factors in European populations have been well  
described, there are few epidemiologic studies regarding risk factors for endometrial can-  
cer in Japanese women. This hospital-based case-control study among Japanese women  
was carried out from 1998 to 2000. The cases were selected from women with endometri-  
al cancer ( $n = 155$ ), and the controls selected from women attending the university gynecol-  
ogical outpatient clinic for cervical cancer screening ( $n = 96$ ). Subjects were interviewed  
to ascertain breast feeding practices, contraceptive usage, as well as potential risk factors  
for endometrial cancer. We observed a lower risk of endometrial cancer associated with  
oral contraceptive (OC) and a higher risk associated with higher body mass index (BMI),  
and older ages at first and last delivery. Gravity reduced odds ratio (OR) for endometrial  
cancer to 0.34 (95% confidence interval [CI] 0.13-0.92). Compared with parous women  
who had never breastfed, the multivariate OR for women with a history of breastfeeding  
was 0.37 (95% CI, 0.17-0.82). Additionally, a greater lapse of time since breastfeeding  
increased OR for endometrial cancer by over three times. In conclusion, the present study  
has indicated that breastfeeding reduces the risk of endometrial cancer in Japanese women.

———— endometrial cancer; breastfeeding; risk factor; case-control study

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Correspondence: Nobuo Yaegashi, Department of Obstetrics and Gynecology, Tohoku University Graduate  
School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

e-mail: yaegashi@mail.tains.tohoku.ac.jp

Age-adjusted incidence rates for endometrial cancer have doubled during the past two decades among Japanese women. The rising incidence possibly may be due to changes in lifestyle, or changes in reproductive factors such as childbearing and contraception, as these characteristics have been associated with endometrial cancer risk in Western populations. In Western countries, there is considerable evidence that reproductive factors play a role in the etiology of endometrial cancer. Nulliparity and obesity have been associated with a higher risk, whereas oral contraceptive (OC) use has been associated with a lower risk (Kirschner et al. 1981; Kelsey et al. 1982; Zumoff 1982; Austin et al. 1991; Schapira et al. 1991; Brinton et al. 1992; Shu et al. 1992; Kalandidi et al. 1996; McPherson et al. 1996; Iemura et al. 2000; Herrinton et al. 2001). A few studies have examined the association between breastfeeding and endometrial cancer risk (Rosenblatt and Thomas 1995; Salazar-Martinez et al. 1999; Newcomb and Trentham-Dietz 2000); however, the findings from these studies are inconsistent.

The reproductive characteristics of Japanese women, however, are different from those of Western populations. For instance, 15%, 36%, and 59% of contraceptive-using women choose OCs in the United States, France, and Germany, respectively, whereas the prevalence of OC use is only 1.5% among Japanese women who use contraception. Only 1.8% of Japanese women older than 50 years have used hormone replacement therapy (HRT), whereas the prevalence of HRT usage is 53% among US women aged 50-59 years. These differences make it difficult to generalize findings obtained in Western studies to Japanese women. There have, however, been a few studies evaluating risk factors for endometrial cancer in Japanese women (Inoue et al. 1994; Hirose et al. 1996, 1999). Therefore, this study was undertaken to further characterize endometrial cancer risk factors in Japanese population.

#### SUBJECTS AND METHODS

This case-control study was a collaborative investigation in three areas of Japan (Tokyo, Kanagawa, and Miyagi). Cases were accrued from three university hos-

pitals from January 1, 1998, through December 31, 2000. Eligible cases included Japanese women between 20 and 80 years of age who underwent surgery for a diagnosis of endometrioid endometrial cancer confirmed by histology. The cases resided in defined geographic catchment areas, and had not received treatment previously. One hundred sixty seven cases were eligible for the study and 12 subjects refused to participate. Thus, 155 (93%) of the eligible cases participated. Stage distribution of the cases was as follows: stage I,  $n = 104$ ; stage II,  $n = 14$ ; stage III,  $n = 33$ ; and stage IV,  $n = 4$ .

The controls were selected from women who attended gynecologic outpatient clinics in the university hospitals for cervical cancer screening. Controls included only women with intact uteri. Ninety six women were included as controls; however, 9 women refused participation (participation rate, 91%). Cases and controls were not matched in terms of age or other variables.

The protocol for this study was approved by the Ethics Committee at Tohoku University Graduate School of Medicine (Sendai, Japan).

Gynecologists interviewed the cases and controls using a standard questionnaire asking about demographic information, medical history, cigarette use, and reproductive history (parity, gravidity, and ages at first pregnancy, last delivery, menarche, menopause, and lactation). Body mass index (BMI) was calculated based on self-reports of weight (kg)/height (m)<sup>2</sup>. The distribution of continuous variables was examined among cases and controls and divided into two or three categories.

To estimate the risk of endometrial cancer associated with various factors, we calculated age-adjusted and multivariate odds ratio (ORs) along with 95% confidence interval (CI) using unconditional logistic regression analysis. Statistical Analysis System (SAS Institute, Cary, NC, USA) software was used for all statistical analyses.

#### RESULTS

The mean ages of cases and controls were 56.1 years and 49.6 years, respectively. Table 1 presents age-adjusted ORs and 95% CIs of the selected variables for the risk of endometrial cancer. Higher BMI was associated with higher risk ( $p = 0.01$ ). OC use was associated with a lower risk of disease (OR, 0.16; 95% CI, 0.04-0.66), although only three cases and ten controls used OCs. Intra-uterine device use, history of HRT, smoking, sterility, hypertension, diabetes mellitus,

TABLE 1. *Baseline characteristics of cases and controls*

Characteristics	Cases	%	Controls	%	Age-adjusted OR	95% CI	<i>p</i> value
Age (years)							
< 45	15	9.7	39	40.6			
45-55	52	33.6	23	24			
55-65	55	35.4	24	25			
≥ 65	33	21.3	10	10.4			
BMI (kg/m <sup>2</sup> )							
< 20.04	36	23.3	26	27.1	1.00		
20.04-21.63	27	17.4	35	36.5	0.47	0.22-0.99	
21-64-23.92	45	29.0	20	20.8	1.24	0.58-2.67	
≥ 23.93	47	30.3	15	15.6	1.92	0.86-4.30	0.01
Oral contraceptive use							
Never	152	98.1	86	89.6	1.00		
Ever	3	1.9	10	10.4	0.16	0.04-0.66	0.01
IUD use							
Never	148	95.5	90	93.8	1.00		
Ever	7	4.5	6	6.2	0.54	0.17-1.71	0.29
HRT use							
Never	132	85.16	85	88.5	1.00		
Ever	23	14.84	11	11.5	1.4	0.63-3.14	0.41
Cigarette smoking							
Never	126	81.3	77	80.2	1.00		
Ever	29	18.7	19	19.8	1.30	0.65-2.61	0.52
Sterility							
Never	143	92.3	87	90.6	1.00		
Ever	12	7.7	9	9.4	0.81	0.31-2.11	0.66
Hypertension							
Never	115	74.2	87	90.6	1.00		
Ever	40	25.8	9	9.4	2.15	0.95-4.86	0.45
Diabetes mellitus							
Never	139	89.7	92	95.8	1.00		
Ever	16	10.3	4	4.2	1.82	0.56-5.92	0.32
Personal cancer history							
Never	139	89.7	92	96.8	1.00		
Ever	16	10.3	4	4.2	1.78	0.55-5.73	0.33

and personal cancer history were not associated with risk. There were 20 persons who had personal cancer history. Among them 11 persons had breast cancer and the remaining nine persons had cancer history at various sites, such as colon can-

cer, rectal cancer, thyroid cancer, gastric cancer, lung cancer, and ovarian cancer. Four of the 20 persons had hormone therapy.

Table 2 shows the ORs for the association of endometrial cancer with reproductive factors.

TABLE 2. *Multivariate Odds Ratio and 95% Confidence Intervals for Endometrial Cancers-According to Reproductive Factors*

Variables	Cases	%	Controls	%	OR*	95% CI	<i>p</i> value
Menopausal status							
Pre	51	32.9	55	57.3	1.00		
Post	104	67.1	41	42.7	0.91	0.39-2.14	0.82
Gravidity							
Never	20	12.9	9	9.4	1.00		
Ever	135	87.1	87	90.6	0.34	0.13-0.92	0.03
No. of pregnancies							
0	20	12.9	9	9.4	1.00		
1	27	17.4	16	16.7	0.43	0.14-1.33	
2	42	27.1	32	33.3	0.34	0.12-0.97	
≥ 3	66	42.6	39	40.6	0.29	0.10-0.85	0.04
Parity							
Never	36	23.2	21	21.9	1.00		
Ever	119	76.8	75	78.1	0.46	0.22-0.96	0.04
No. of deliveries							
0	36	23.2	21	21.9	1.00		
1	29	18.7	18	18.8	0.45	0.18-1.12	
2	68	43.9	44	45.8	0.47	0.21-1.04	
≥ 3	22	14.2	13	13.5	0.44	0.16-1.20	0.1
Age at first delivery**							
≤ 24	43	36	11	14.7	1.00		
25-26	36	30.3	23	30.7	0.45	0.18-1.10	
27-29	21	17.7	23	30.7	0.30	0.12-0.78	
≥ 30	19	16	18	24	0.35	0.13-0.96	0.05
Age at last delivery**							
≤ 25	23	19.3	6	8	1.00		
26-30	40	33.6	25	33.3	0.48	0.16-1.45	
31-33	39	32.8	26	34.7	0.45	0.15-1.36	
≥ 34	17	14.3	18	24	0.28	0.08-0.94	0.02

\* OR adjusted for age, BMI, and oral contraceptive use.

\*\* Parous women only.

The ORs were adjusted for age, BMI, and OC use. Gravidity was inversely associated with endometrial cancer risk. Women who reported ever being pregnant had only one third the risk of endometrial cancer compared with women who had never been pregnant (OR, 0.34; 95% CI, 0.13-0.92,  $p = 0.03$ ). Women who reported three or more pregnancies had about one third the risk of women with no pregnancies (OR, 0.29; 95% CI, 0.10-0.85).

Parity was also inversely associated with endometrial cancer risk. Women who reported ever having delivery had about one half the risk of endometrial cancer compared with women who had never delivered (OR, 0.46; 95% CI, 0.22-0.96,  $p = 0.04$ ). Higher age at the first or last deliveries was associated with a lower risk for endometrial cancer ( $p = 0.05$ ,  $p = 0.02$ ). Age at menarche, menopausal status, age at menopause, history of dysmenorrhea, and history of abortion were not associated with risk (data not shown).

Only parous women, representing 119 cases and 75 controls, were included in the analysis of the association between breastfeeding and endometrial cancer risk presented in Table 3. Table 3 also showed the age distribution of both cases and control and that of the lapse of the last breastfeeding. The ORs were adjusted for age, BMI, and OC use as shown in Table 3. Compared with parous women who had never breastfed, the mul-

tivariate odds ratio for women who had ever breastfed was 0.37 (95% CI: 0.17-0.82,  $p = 0.013$ ). A greater lapse of time since breastfeeding concluded was directly associated with an increased risk of endometrial cancer (OR of 20-29 years, 3.10, 95% CI: 1.14-8.48, and OR of 30 or longer, 3.85, 95% CI: 1.00-14.84,  $p = 0.045$ ). Then, we analyzed the association between frequency or duration of breastfeeding and endometrial cancer risk, but did not find any significant association (data not shown).

## DISCUSSION

In this hospital-based case-control study among Japanese women, we observed a lower risk of endometrial cancer associated with OC use and gravidity, and a higher risk associated with higher BMI, older ages at first and last delivery and number of pregnancies. These findings were consistent with data obtained in prior Japanese studies (Inoue et al. 1994; Hirose et al. 1996, 1999). In contrast to the study by Inoue et al. (1994), our study failed to demonstrate an association between a history of hypertension, diabetes mellitus, or cancer.

Our study also demonstrated a reduction in the risk of endometrial cancer associated with breastfeeding. The proportion of never breastfeeding (35.3%) in endometrial cancer cases was larger than that in control, but the risk was signifi-

TABLE 3. *Multivariate Odds Ratio for Endometrial Cancers in relation to breastfeeding and age among parous women*

Variables	Cases (n)					Controls (n)					OR*	95% CI	p value
	Total	< 45	45-55	55-65	65 ≤	Total	< 45	45-55	55-65	65 ≤			
breastfeeding													
Never	42	1	10	24	7	11	3	3	2	3	1.00		
Ever	77	1	31	26	19	64	25	14	18	7	0.37	0.17-0.82	0.013
Years since last breastfed**													
1-19	12	1	9	1	1	33	24	7	2	0	1.00		
20-29	31	0	17	12	2	20	1	7	11	1	3.10	1.14-8.48	
≥ 30	34	0	5	13	16	11	0	0	5	6	3.85	1.00-14.84	0.045

\* Adjusted for age, BMI and oral contraceptive use.

\*\* Ever breastfed women only.

cant even after been adjusted for age, BMI, and contraceptive use. The risk reduction of endometrial cancer was associated not only with breastfeeding itself but also with time since the last breastfeeding. From 1982 to 2000, seven case-control studies conducted in six countries, including four developing countries, examined the relationship between breastfeeding and the risk of endometrial cancer. Four early studies, two of which were Japanese, failed to support an association (Kelsey et al. 1982; Brinton et al. 1992; Hirose et al. 1996, 1999). Three recent Western studies, however, suggested a protective effect of breastfeeding (Rosenblatt and Thomas 1995; Salazar-Martinez et al. 1999; Newcomb and Trentham-Dietz 2000). This effect was more pronounced with recent breastfeeding, diminishing as the history of breastfeeding became more remote (Rosenblatt and Thomas 1995; Newcomb and Trentham-Dietz 2000). Our findings were consistent with those of the latter studies, making this the first report that notes an inverse association between breastfeeding and the risk of endometrial cancer among Japanese women.

Exposure of the endometrium to estrogen in the absence of progesterone is thought to increase the risk of endometrial cancer (Key and Pike 1988- see comment for citation). In lactating women, the ovarian cycle is suppressed and blood estrogen levels are reduced (Baird et al. 1979). In the case of oral contraceptives, progesterone continually opposes estrogen, minimizing the duration of time the endometrium is exposed to unopposed estrogen. Thus, suppression of circulating estrogen levels, or opposition of estrogen by progesterone, may represent a biological mechanism accounting for the protective effects of pregnancy, oral contraceptives, and breastfeeding against carcinogenesis of endometrial tissue.

Among Japanese women, the birth rate decreased 28.1 to 9.3 per 1,000 during 1950-2000, and the proportion of women who exclusively breastfed decreased from 70.5% to 44.8% during the same period (Kaneda 2003). In our study, the proportion of women who breastfed for 13 months was 52.4%. The observed lower risk associated with breastfeeding in this study sug-

gests that the recent increase in incidence of endometrial cancer in Japan may be in part attributed to a decrease in both the number of pregnancies and the prevalence of breastfeeding.

A limitation of this study was its lack of age matching. This resulted in a mean age of cases that was 6 years older than that of controls. It is unlikely that the lack of age matching resulted in serious distortion of our observations because all analyses were adjusted for continuous age. Furthermore, the findings in these studies were consistent with data obtained in several previous studies. Another limitation of the study was the small number of control. To overcome these limitations, in progress is our new case control study which matched ages of cases and controls and included two times more subjects of control. These data will confirm the present observations.

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