

## Anthropometric and Other Risk Factors for Ovarian Cancer in a Case-Control Study

Mitsuru Mori,<sup>1</sup> Takashi Nishida,<sup>3</sup> Toru Sugiyama,<sup>3</sup> Kan Komai,<sup>3</sup> Michiaki Yakushiji,<sup>3</sup> Koichi Fukuda,<sup>2</sup> Toshimitsu Tanaka,<sup>2</sup> Masatoshi Yokoyama<sup>2</sup> and Hajime Sugimori<sup>2</sup>

<sup>1</sup>Department of Community Health Science, <sup>2</sup>Department of Obstetrics and Gynecology, Saga Medical School, 5-1-1 Nabeshima, Saga 849 and <sup>3</sup>Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830

Because it has been suggested that an environmental factor may play a role in the etiology of ovarian cancer, a case-control study was conducted to assess some environmental and other risk factors for ovarian cancer from 1994 to 1996 in northern Kyushu, Japan. We analyzed the data of 89 cases with epithelial ovarian cancer and 323 controls without any cancer or ovarian disorder. After controlling for the effect of potential confounders, the odds ratios of ovarian cancer across increasing quartiles of the heaviest body weight were 1.00, 1.15, 1.71, 2.29 ( $P=0.008$ , test for trend). Significantly increased risks were noted for a history of diabetes mellitus ( $P<0.05$ ), and for a family history of ovarian cancer ( $P<0.05$ ). Significantly decreased trends for risk were obtained for the number of pregnancies ( $P<0.01$ ) and the number of live births ( $P<0.001$ ). This study provides additional support for an association between obesity and the risk of ovarian cancer. This relationship may at least partly explain the recent increase in the incidence of ovarian cancer in Japan, although possible contributions of other factors can not be ruled out.

Key words: Ovarian neoplasms — Case-control study — Obesity — Familial history — Reproductive history

The age-adjusted mortality rate of ovarian cancer has been rising since the 1960's in Japan,<sup>1)</sup> and the age-adjusted incidence of the disease in Japan has increased from 3.7 per 10<sup>5</sup> in 1966 to 7.0 per 10<sup>5</sup> in 1989.<sup>1)</sup> Although the age-adjusted incidence of ovarian cancer among Japanese in Japan (5.1 per 10<sup>5</sup> during 1984 and 1986) was lower than that among white people in Los Angeles, USA (12.1 per 10<sup>5</sup>), the rate among Japanese immigrants in Los Angeles (10.7 per 10<sup>5</sup>) was twice as high as that among Japanese in Japan.<sup>2)</sup> These figures suggested that an environmental factor may play a role in the etiology of ovarian cancer.

Anthropometric dimensions and dietary habits are possible candidates for involvement in the etiology of ovarian cancer. The average body weight of Japanese women aged 40 to 49 years has increased from 51.7 kg in 1969 to 54.6 kg in 1995,<sup>3)</sup> and obesity has been indicated to be associated with the risk of ovarian cancer.<sup>4-9)</sup> Likewise, Japanese have doubled their consumption of animal fat from 14.3 g per day per capita in 1965 to 28.5 g in 1994,<sup>3)</sup> and a diet high in animal fat and meat has been suggested to be related to the risk of ovarian cancer, as well.<sup>10-13)</sup> However, somatometric and dietary risk factors have yet to be firmly implicated in the etiology of this disease.

In the present case-control study, we assessed the relationship of ovarian cancer risk with some anthropometric factors and dietary history. In addition, we examined the

risks associated with reproductive history, family history of cancer, and other factors addressed in previous studies.

### MATERIALS AND METHODS

All histologically confirmed cases of malignant or borderline malignant ovarian cancer were registered for the survey at 3 major gynecological-oncological hospitals (Kurume University School of Medicine, Kurume University Medical Center, and Saga Medical School) in the Chikugo-Saga Counties of northern Kyushu, Japan, between October, 1994 and July, 1996. In total, 111 ovarian cancer cases were enrolled in the study, and the survey was completed for all of the cases. The analysis was restricted to 89 cases whose cancer originated from the common epithelium of the ovary and who had been diagnosed within 5 years prior to the interview.

In Japan, most women aged 30 years or over are invited to participate in a uterine cancer screening test, and around 25% of them take part in the test annually. Controls were chosen from participants in the tests which were carried out administratively in the 2 cities and 1 town in the Chikugo-Saga Counties in northern Kyushu between April and August of 1995. The sample was frequency-matched by age within the groupings of 30–39, 40–49, 50–59, 60–69, and 70–85 years to the expected distribution of case subjects. In total, 335 controls were

enrolled in the study, and the survey was completed for all of the enrolled controls. Exclusion criteria for the control group included having had any cancer or ovarian disorder, and 12 controls were excluded on this basis.

Informed consent was obtained from both the cases and controls before the survey. A trained interviewer (the first author) administered a standard questionnaire in a face-to-face interview either in the hospitals (cases) or in the institutions where screening tests for uterine cancer were performed (controls). Questions were asked about education and occupation, marital status, cigarette and alcohol consumption, body height and weight, past history, family history, menstruation, postmenopausal status, pregnancy and parity, lactation, contraception, and infertility. Cases and controls were asked whether they had had nearly daily consumption of milk, meat, and miso soup in their teens and twenties. Miso is fermented soybean paste, and miso soup is a typical Japanese dish usually taken with a

bowl of rice at meals. There were 85 questions in the questionnaire, and the average duration of the interview was 7.1 min (standard deviation, 1.9 min).

An adjusted odds ratio (OR) and its 95% confidence interval (95% CI) were estimated with the multivariate unconditional logistic regression model.<sup>14)</sup> The SAS computer program was employed for the analysis.<sup>15)</sup> Both trend in the ORs with exposure (parameter estimates of slope) and ORs by categories were examined. In the case of continuous variables, the trends of effects were reported based on units of approximately the 25th, 50th, and 75th percentiles of the combined case-control distribution. Age was included in all models as a continuous variable. Tests of statistical significance were based on two-sided *P* values, and the  $\alpha$ -error was set at the 5% level or below.

It has been reported that the proportion of women who had married among the participants in uterine cancer

Table I. Age-adjusted Odds Ratios (with 95% Confidence Intervals) of Education and Occupation, Marital Status, Smoking and Drinking, and History of Dietary Habits

Factor	Cases (n=89)	Controls (n=323)	Odds ratio
Education and occupation			
Mean age at last school graduation (SD <sup>a)</sup> )	17.4 years (2.0)	17.5 years (2.0)	1.02 (0.91–1.18)
Professional work	17 (19.1%)	39 (12.1%)	1.86 (0.98–3.50)
Blue-collar work	30 (33.7%)	129 (39.9%)	0.67 (0.40–1.13)
Marital status			
Never-married	9 (10.1%)	9 ( 2.8%)	3.92** (1.50–10.26)
Married	57 (62.9%)	261 (80.8%)	0.42** (0.24–0.75)
Widowed	21 (26.3%)	47 (14.5%)	1.54 (0.79–3.00)
Divorced or separated	3 ( 3.8%)	6 ( 1.9%)	1.97 (0.48–8.11)
Mean age at marriage (SD <sup>a)</sup> ) (Excluding never-married women <sup>b)</sup> )	23.7 years (3.2)	23.9 years (3.1)	0.99 (0.91–1.07)
Smoking and drinking			
Daily cigarette consumption (Currently or stopped)	10 (11.2%)	26 ( 8.1%)	1.64 (0.75–3.59)
Alcohol consumption more than once a week (Currently or stopped)	34 (38.2%)	149 (46.1%)	0.78 (0.48–1.27)
Father's habitual smoking	61 (70.9%)	217 (72.3%)	1.03 (0.60–1.77)
Mother's habitual smoking	4 ( 4.5%)	23 ( 7.2%)	0.55 (0.19–1.66)
Husband's habitual smoking (Excluding never married women <sup>b)</sup> )	60 (75.0%)	212 (67.5%)	1.46 (0.84–2.56)
Daily consumption of foods in teens and twenties			
Milk in teens	12 (13.5%)	78 (24.2%)	0.55 (0.28–1.07)
Milk in twenties	9 (10.1%)	61 (18.9%)	0.55 (0.25–1.18)
Meat in teens	6 ( 6.8%)	34 (10.5%)	0.69 (0.28–1.73)
Meat in twenties	10 (11.2%)	50 (15.5%)	0.79 (0.37–1.65)
Miso soup in teens	12 (13.5%)	77 (24.2%)	0.56 (0.28–1.12)
Miso soup in twenties	74 (83.2%)	259 (80.7%)	1.07 (0.57–2.01)

a) Standard deviation.

b) Based on 80 cases and 314 controls excluding never-married women.

\*\* *P*<0.01.

Table II. Odds Ratios (with 95% Confidence Intervals) of Body Height, Body Weight and Body Mass Index Analyzed Adjusting for Age and Marital Status

Factor	Cases (n=89)	Controls (n=323)	Odds ratio
Body height (cm)			
-149.9	24 (27.0%)	87 (26.9%)	1.00
150.0-152.9	25 (28.0%)	64 (19.8%)	1.59 (0.81-3.15)
153.0-157.9	19 (21.4%)	94 (29.1%)	0.94 (0.46-1.94)
158.0-	21 (23.6%)	78 (24.2%)	1.37 (0.63-3.01)
test for trend per category			P=0.77
Body weight at 20 years of age (kg)			
-44.9	24 (27.0%)	90 (27.8%)	1.00
45.0-48.9	22 (24.7%)	74 (22.9%)	1.18 (0.60-2.29)
49.0-54.9	19 (21.3%)	99 (30.7%)	0.78 (0.39-1.53)
55.0-	24 (27.0%)	60 (18.6%)	1.52 (0.78-2.96)
test for trend per category			P=0.49
Body weight before diagnosis (kg)			
-46.9	26 (29.2%)	72 (22.3%)	1.00
47.0-52.9	23 (25.8%)	95 (29.4%)	0.70 (0.36-1.34)
53.0-56.9	18 (20.2%)	83 (25.7%)	0.57 (0.28-1.16)
57.0-	22 (24.8%)	73 (22.6%)	0.92 (0.47-1.80)
test for trend per category			P=0.68
The heaviest nonpregnant body weight (kg)			
-52.9	18 (20.2%)	93 (28.8%)	1.00
53.0-56.9	22 (24.7%)	97 (30.0%)	1.15 (0.57-2.34)
57.0-60.9	21 (23.6%)	65 (20.1%)	1.71 (0.83-3.50)
61.0-	28 (31.5%)	68 (21.1%)	2.29* (1.15-4.57)
test for trend per category			P=0.008
Body mass index calculated from the heaviest nonpregnant body weight			
-21.9	19 (21.4%)	87 (26.9%)	1.00
22.0-23.8	18 (20.2%)	87 (26.9%)	0.89 (0.44-1.82)
23.9-25.8	23 (25.8%)	76 (23.6%)	1.21 (0.61-2.42)
25.9-	29 (32.6%)	73 (22.6%)	1.55 (0.80-3.01)
test for trend per category			P=0.11

\* P<0.05.

screening was higher than that among non-participants.<sup>16)</sup> Because the source of the control group was the participants in uterine cancer screening in our study, and the proportion of married women was significantly lower among the cases than that among the controls, as shown later, we suspected that marital status may confound the findings. Accordingly, we included the variable of marital status as having married=1 and never having married=0 in the model for most of the following analyses. We have not shown the results without adjustment for marital status, since we found these results to be essentially the same with and without the adjustment, in terms of statistical significance.

## RESULTS

The mean age at the interview was 56.2 years (standard deviation, SD=12.7 years: range, 32-84 years) for the 89

cases and 53.7 years (SD=53.7 years: range, 30-82 years) for the 323 controls. Seventy-five (84.3%) and 84 (94.4%) of the cases were interviewed within one year and 3 years of the initial diagnosis, respectively. The cases consisted of 83 malignant and 6 borderline-malignant adenocarcinomas with the following histopathologic classifications: 38 serous, 14 mucinous, 14 endometrioid, 19 clear cell, and 4 unspecified.

Table I shows the age-adjusted ORs of education and occupation, marital status, smoking and drinking, and dietary habits in their teens and twenties. No substantial differences were observed between cases and controls with regard to educational years, occupation held for the longest period of time, habits of cigarette and alcohol consumption, and exposure to environmental tobacco smoke brought about either by a father, a mother, or a husband. The proportion of never-married women was significantly higher among the cases than among the con-

Table III. Odds Ratios (with 95% Confidence Intervals) of Past History, Family History, Menstruation and Postmenopausal Status Analyzed Adjusting for Age and Marital Status

Factor	Cases (n=89)	Controls (n=323)	Odds ratio
<b>Past history</b>			
Hypertension	14 (15.7%)	42 (13.0%)	1.04 (0.52–2.07)
Diabetes mellitus	7 ( 7.9%)	8 ( 2.5%)	3.21* (1.11–9.30)
Allergic diseases	17 (19.1%)	68 (21.1%)	0.88 (0.48–1.61)
Any surgery	46 (51.7%)	152 (47.1%)	1.15 (0.71–1.85)
<b>Family history in parents or siblings</b>			
Ovarian cancer	5 ( 5.6%)	3 ( 0.9%)	6.80* (1.58–29.29)
Breast cancer	2 ( 2.3%)	10 ( 3.1%)	0.78 (0.17–3.65)
Uterine cancer	5 ( 5.6%)	10 ( 3.1%)	1.83 (0.60–5.55)
Colorectal cancer	8 ( 9.0%)	12 ( 3.7%)	2.31 (0.89–5.98)
Any other cancer	24 (27.0%)	92 (28.5%)	0.90 (0.52–1.53)
<b>Menstruation</b>			
Mean age at menarche (SD <sup>a</sup> )	14.1 years (2.2)	13.9 years (1.7)	0.98 (0.85–1.14)
Amenorrhea	6 ( 6.7%)	30 ( 9.3%)	0.77 (0.30–1.95)
Irregularity	16 (18.0%)	53 (16.4%)	1.09 (0.57–2.07)
Hormonal therapy for amenorrhea or irregularity	6 ( 6.7%)	12 ( 3.7%)	1.99 (0.69–5.74)
Menopause	55 (61.8%)	180 (55.7%)	0.76 (0.34–1.69)
<b>Menopausal status (Excluding premenopausal women<sup>b</sup>)</b>			
Mean age at menopause (SD <sup>a</sup> )	49.0 years (4.0)	48.9 years (3.5)	1.00 (0.92–1.09)
Menopause by surgery	4 ( 7.3%)	6 ( 3.3%)	2.23 (0.57–8.66)
Postmenopausal symptoms	8 (14.6%)	30 (16.7%)	1.03 (0.43–2.44)
Hormone replacement therapy for postmenopausal symptoms	1 ( 1.8%)	8 ( 4.4%)	0.56 (0.07–4.77)

a) Standard deviation.

b) Based on 55 cases and 180 controls excluding premenopausal women.

\*  $P < 0.05$ .

controls (OR=3.92, 95%CI 1.50–10.26,  $P < 0.01$ ), and conversely, the proportion of women who had been married was significantly lower among the cases than among the controls (OR=0.42, 95%CI 0.24–0.75,  $P < 0.01$ ). Age at marriage did not differ between the cases and the controls. The proportions having daily consumption of milk in their teens and twenties were somewhat lower in the cases than in the controls, but the values were not significantly different. Similarly, the proportions of individuals having daily consumption of meat and miso soup either in their teens or twenties did not differ between the 2 groups.

Table II shows the ORs of body height, body weight, and body mass index analyzed with adjustments for age and marital status. The ORs of ovarian cancer across increasing quartiles of the heaviest nonpregnant body weight were 1.00, 1.15, 1.17, 2.29 ( $P = 0.008$ , test for trend per category). A non-significant increased trend was noted for body mass index (BMI) calculated from the heaviest body weight in kilograms divided by the square of the height in meters ( $P = 0.11$ , test for trend per category).

Obese premenopausal women frequently have anovulatory cycles, for which reason they may have difficulty in conceiving.<sup>17</sup> Therefore, we calculated the OR of the

heaviest body weight by adjusting for the number of parities as well as age. The positive trend for the risk was still significant when observed across increasing quartiles of the heaviest body weight (OR=1.00, 1.09, 1.64, 2.08,  $P = 0.018$ ). The cases and the controls did not differ either in body height, body weight at 20 years of age, or body weight before initial diagnosis.

Table III shows the ORs of past medical history, family history, menstruation, and postmenopausal status analyzed adjusting for age and marital status. A history of diabetes mellitus was associated with a significantly increased risk of ovarian cancer (OR=2.94, 95%CI 1.02–8.47,  $P < 0.05$ ). However, when the heaviest weight was simultaneously included in the model as a continuous variable, the OR for a history of diabetes mellitus became insignificant (OR=2.52, 95%CI 0.86–7.40).

A history of ovarian cancer was found significantly more frequently in first degree relatives of the cases (5.6%; 1 mother and 4 sisters) than in those of the controls (0.9%; 1 mother and 2 sisters) (OR=6.80, 95%CI 1.58–29.29,  $P < 0.05$ ). The average age at diagnosis for the 5 cases with a family history of ovarian cancer (55.4 years) was not significantly different from that for the

Table IV. Age-adjusted Odds Ratios (with 95% Confidence Intervals) of Pregnancy and Parity Analyzed Excluding Never-married Women<sup>b)</sup>

Factor	Cases	Controls	Odds ratio
<b>Pregnancy</b>			
Number of pregnancies			
0	8 ( 9.3%)	9 ( 2.9%)	1.00
1-2	23 (26.7%)	68 (21.7%)	0.34 (0.11-1.02)
3-4	31 (36.1%)	127 (40.5%)	0.25** (0.09-0.72)
5 or more	24 (27.9%)	110 (35.0%)	0.19** (0.06-0.55)
test for trend per category			<i>P</i> <0.01
Mean age at the first pregnancy (SD <sup>d)</sup> (Excluding never-pregnant women <sup>c)</sup> )	24.4 years (3.0)	24.9 years (3.3)	0.98 (0.89-1.05)
Twin pregnancy	0 ( 0.0%)	5 ( 1.6%)	— (—)
Induced abortion	39 (48.8%)	151 (48.1%)	0.95 (0.58-1.57)
Spontaneous abortion	19 (23.8%)	94 (29.9%)	0.72 (0.41-1.27)
<b>Parity</b>			
Number of live births			
0	12 (15.0%)	11 ( 3.5%)	0
1-2	37 (46.3%)	138 (44.0%)	0.24** (0.10-0.61)
3-4	28 (35.0%)	149 (47.5%)	0.15*** (0.06-0.38)
5 or more	3 ( 3.8%)	16 ( 5.1%)	0.11** (0.02-0.46)
test for trend per category			<i>P</i> <0.001
Mean age at the first live birth (SD <sup>d)</sup> (Excluding non-parous women <sup>d)</sup> )	24.7 years (3.1)	25.3 years (3.3)	0.95 (0.87-1.04)

a, b) See Table I.

c) Based on 72 cases and 307 controls excluding non-pregnant women.

d) Based on 68 cases and 304 controls excluding non-parous women.

(There was a control subject who had never married but had experienced a pregnancy, and another control subject who had never married but had had a live birth.)

\*\* *P*<0.01. \*\*\* *P*<0.001.

Table V. Age-adjusted Odds Ratios (with 95% Confidence Intervals) of Lactation, Contraception, and Infertility

Factor	Cases	Controls	Odds ratio
<b>Lactation (Excluding non-parous women<sup>d)</sup>)</b>			
Had breast-fed a child	63 (92.7%)	288 (95.1%)	0.59 (0.21-1.72)
Mean duration of breast-feeding per child (SD <sup>d)</sup> )	9.2 months (6.7)	8.5 months (6.1)	1.00 (0.96-1.05)
<b>Contraception (Excluding never-married women<sup>b)</sup>)</b>			
Oral contraceptives	2 ( 2.5%)	22 ( 7.0%)	0.38 (0.09-1.66)
Intrauterine devices	9 (11.3%)	51 (16.2%)	0.64 (0.30-1.35)
Condom	43 (53.8%)	198 (63.1%)	0.78 (0.46-1.33)
Pessary	5 ( 6.3%)	15 ( 4.8%)	1.18 (0.41-3.39)
Tubal sterilization	6 ( 7.5%)	24 ( 7.6%)	0.92 (0.36-2.35)
Husband's vasectomy	2 ( 2.5%)	5 ( 1.6%)	1.72 (0.33-9.10)
<b>Infertility (Excluding never-married women<sup>b)</sup>)</b>			
Clinically diagnosed infertility in a subject	8 (10.0%)	40 (12.7%)	0.82 (0.37-1.84)
Hormonal therapy for infertility	6 ( 7.5%)	23 ( 7.3%)	1.18 (0.46-3.07)
Clinically diagnosed infertility in husband of a subject	3 ( 3.8%)	3 ( 1.0%)	4.78 (0.93-24.51)

a, b) See Table I.

d) See Table IV.

residual cases (56.2 years). A history of colorectal cancer was found to be more prevalent in first degree relatives of the cases (9.0%) than in those of the controls (3.7%), but the difference was not significant. There was no association of a family history of breast, uterine, or any other cancer with the risk of ovarian cancer. No substantial differences were observed between cases and controls with regard to variables related to menstruation and menopausal status.

Table IV shows the age-adjusted ORs of pregnancy and parity analyzed after exclusion of women who had never married. As compared with that in women who had never been pregnant, the risk of ovarian cancer declined significantly with increasing number of pregnancies ( $P < 0.01$ , test for trend per category). Likewise, the risk of ovarian cancer was strongly associated with a decreased number of live births ( $P < 0.001$ , test for trend per category). Induced or spontaneous abortion, age at first pregnancy, and age at the first live birth were not associated with the risk of ovarian cancer.

Table V shows the age-adjusted ORs of lactation, contraception, and infertility analyzed excluding non-parous women and women who had never married. Experience in lactation or duration of lactation per child did not differ between the cases and the controls. The cases used less oral contraceptives than the controls, but the difference was not significant.

## DISCUSSION

This case-control study on ovarian cancer had high response rates among cases and controls and strict compatibility of interviews conducted in person. However, because the sample size was limited,  $\beta$ -error might exist in this study. Given that the proportion of persons exposed to a variable was 20% in the general population, the relative risk of the variable was 2.5, and the two-sided  $\alpha$ -error was 0.05, the two-sided  $\beta$ -error (1-power) was calculated to be 0.17 for this study.

In an earlier study,<sup>16)</sup> it was shown that, compared to non-participants in uterine cancer screening, participants had a larger proportion of individuals who had married, a smaller proportion of smokers, and a larger proportion who consumed milk daily. In our study, the case group was essentially similar to the control group with regard to smoking habits and daily consumption of milk in their teens and twenties, but there were significantly more women who had married in the cases than in the controls. Accordingly, we included the variable of marital status in the model for the analyses, although the possibility of a selection bias can not be totally ruled out.

Ovarian cancer risk appeared to increase with the heaviest body weight, and this association could not be attributed to the reduced number of parities. Several pre-

vious studies have shown a positive association of obesity<sup>4-9)</sup> as well as a high waist-to-hip ratio<sup>18)</sup> with risk of ovarian cancer. Further, it is probable that our finding of a positive association between a history of diabetes mellitus and the risk of ovarian cancer was a consequence of the effect of obesity. Although some studies failed to find a positive association between obesity and the risk of ovarian cancer, most of these studies, including the one by the first author and his coworkers,<sup>19)</sup> did not examine the heaviest body weight as a risk factor. We think that the heaviest body weight is a reasonable scale to evaluate the effect of body size on cancer risk, because it would not be influenced by loss of weight during the neoplastic process.

Cramer and Welch suggested that the tumorigenesis process occurs in two stages.<sup>20)</sup> In the first stage, inclusion cysts are formed by entrapment of ovarian surface epithelium into ovarian stroma. In the second stage, estrogens, as well as gonadotropins, promote proliferation and malignant transformation of the inclusion cyst. This theory is supported by the identification of estrogen receptors in the cytosol of epithelial ovarian cancer.<sup>21)</sup> Furthermore, estrogens have been experimentally indicated to accelerate 7, 12-dimethylbenz(*a*)anthracene-induced ovarian cancer in rats.<sup>22)</sup>

Obesity has an effect on sex hormones, resulting in an increase of free, biologically active estrogens from extraglandular sources, because it enhances the conversion of both gonadal and adrenal androgens to physiologically active estrogens in peripheral tissues, and reduces serum sex hormone-binding globulin capacity.<sup>23)</sup> Accordingly, obesity could promote tumor development via elevated estrogens.

There is no report, to our knowledge, which shows the difference in body weight between participants and non-participants of a cancer screening test. Moreover, our results indicated no differences in body weight at 20 years of age, or before the diagnosis: the difference was exclusively observed in the heaviest body weight between the cases and the controls. If our results do not represent biased findings, we might infer that increased energy intake and/or sedentary life style during the critical age at onset of ovarian cancer, as reflected in increased body weight, might account for the increased incidence of ovarian cancer over the last few decades in Japan. However, it can not be totally ruled out that the association of heaviest nonpregnant weight with the risk of ovarian cancer was brought about by a bias such as a recall bias.

We believed that dietary habits in the teens and twenties would be crucial for later onset of ovarian cancer. However, several methodological limitations should be considered in interpreting our non-significant results for dietary habits. Firstly, there is some uncertainty in memory about dietary history at those ages. Secondly, because

our questions were restricted to daily consumption of milk, meat, and miso soup, the full range of dietary exposure could not be encompassed. Thirdly, because more of the participants in uterine cancer screening have been reported to drink milk,<sup>16)</sup> the possibility of a selection bias can not be excluded as an explanation of the results on dietary history.

History of ovarian cancer in first degree relatives (a mother or sister) was shown to predict increased risk of ovarian cancer. This is consistent with the widely reported finding of familial clustering of ovarian cancer.<sup>5,9,24-27)</sup> As the population attributable risk percent was estimated to be 7.0 percent in the previous study,<sup>27)</sup> a small fraction of ovarian cancer may occur through genetic mechanisms.

Our results support previous observations of a decrease in ovarian cancer risk with increasing number of pregnancies or live births.<sup>5,6,9,12,18,19,28-31)</sup> This association may occur through a mechanism involving incessant ovulation<sup>32)</sup> and exposure to gonadotropins.<sup>33)</sup> Because neither hypothesis can completely explain this association, Adami and coworkers proposed another hypothesis, that pregnancy clears from the ovaries cells that have undergone malignant transformation.<sup>30)</sup> However, the detailed mechanism is still under consideration. If pregnancy were to reduce directly the risk of ovarian cancer, the decreasing number of pregnancies among Japanese women recently may partly explain the increasing incidence of ovarian cancer.

Oral contraceptives are infrequently used in Japan. An inverse association between use of oral contraceptives and the risk of ovarian cancer was noted in the present study, as in most previous investigations,<sup>5,9,12,29,31,34)</sup> although our result was not statistically significant. A decreased

ovarian cancer risk for women who have undergone tubal sterilization has been reported,<sup>9,12,19,29,35,36)</sup> but we did not find such a relationship in this study. We have indicated, on the basis of meta-analysis, that the inverse association between tubal sterilization and ovarian cancer risk may be an indirect one through subfertility.<sup>37)</sup> Although there are some articles which have shown a positive relationship between the use of fertility drugs<sup>29,38)</sup> or hormone replacement therapy<sup>39)</sup> and the risk of ovarian cancer, this study did not support such relationships.

In conclusion, this study provides additional support for an association between obesity and the risk of ovarian cancer. This relationship may partly explain the recent increase in the incidence of ovarian cancer in Japan, although the possible contribution of other factors such as the decreasing number of live births can not be ruled out. Further epidemiological studies and relevant animal experiments are necessary before any public health recommendations can be made. If our findings are confirmed, however, avoidance of obesity may be a practical means for primary prevention of ovarian cancer.

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