Risk factors for epithelial ovarian cancer in Japan - results from the Japan Public Health Center-based Prospective Study cohort

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Abstract. The aim of this study was to evaluate the risk factors for invasive primary epithelial ovarian cancer among Japanese women. In 1990-1994, 45,748 women aged 40-69 years were enrolled in the Japan Public Health Center-based Prospective Study cohort. Only 86 epithelial ovarian cancer cases were diagnosed during follow-up through 2008, reflecting the low ovarian cancer incidence rates in Japan. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) according to the exposure of interest. The median age at epithelial ovarian cancer diagnosis was 59 years, with a median follow-up before diagnosis of 7.6 years. There were no statistically significant associations for age at menarche or first birth, breastfeeding, use of exogenous hormones, menopausal status at cohort enrollment, height, body mass index, smoking status, second-hand smoke, alcohol consumption, physical activity and family history of cancer in a first-degree relative. The linear decrease in HR associated with each additional birth was 0.75 (95% CI 0.56-0.99). Among women who usually slept >7 h per day, an HR of 0.4 (95% CI 0.2-0.9) emerged compared to those who slept <6 h. This study did not confirm risk factors for epithelial ovarian cancer among Japanese women that have been reported in studies carried out elsewhere. Usual sleep duration of >7 h per day was inversely associated with epithelial ovarian cancer risk, which is a novel finding that needs to be confirmed in other studies.

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Introduction

Ovarian cancer incidence and mortality rates in women in Japan have been increasing in the past decades, as indicated by the National Cancer Center in Tokyo (http://ganjoho.jp/public/statistics/backnumber/2010_en.html). Ovarian cancer incidence rates in Japan (8.1 per 100,000) (1) are higher than worldwide rates, but relatively low compared to rates in Europe and the United States (2,3). Age-standardized mortality rates of ovarian cancer in Japan increased four-fold, from 0.9 to 3.6 per 100,000 women, between the 1950s and the 1990s (4). In the past two decades they have stabilized, reaching 3.3 per 100,000 women in 2004 (5), which is slightly below the worldwide estimates for that year (3.8 per 100,000) (3). Studies on migrants suggest that ovarian cancer incidence rates are higher among Japanese women born in the United States than among those born in Japan (6). The ovarian cancer mortality trends may be explained by birth cohort and period effects in Japan, as mortality has increased within recent birth cohorts for all age groups, with the slope gradually becoming less steep (7).

The historically low rates of ovarian cancer in Japan could offer instructive insights into the etiology of the disease. Individual characteristics, such as reproductive factors [early age at menarche, use of oral contraceptives, late age at menopause, use of estrogen only hormone replacement therapy (HRT), low parity, breastfeeding, age at first and last birth (8-11)], body size (height, weight), lifestyle [smoking (12), alcohol consumption, physical inactivity (13)], and genetic susceptibility (family history of ovarian cancer in a first-degree relative affected at an early age) may be associated with ovarian cancer risk. These associations may differ across populations and ethnic groups, and could partially explain differences in incidence rates across countries. Risk factors for epithelial ovarian cancer among Japanese women have been examined in one prospective cohort study (14-16) besides ours (17), and in several case-control studies (8,18-25), with inconsistent results.

In order to address these issues, we present here data from a prospective cohort study in Japan on the incidence of invasive primary epithelial ovarian cancer in relation to different

potential risk and protective factors that have been reported or hypothesized to be associated with ovarian cancer risk in Western populations.

Subjects and methods

The Japan Public Health Center-based Prospective (JPHC) Study, which began in 1990 for cohort I, and in 1993 for cohort II, included Japanese inhabitants living in the municipalities served by 11 different public health centers (henceforth referred to as study areas). Participants were aged 40-59 years in cohort I, and 40-69 years in cohort II at the time of enrollment.

One study area in cohort I was excluded in this report, due to lack of cancer incidence data. An additional 144 women were considered non-eligible because of non-Japanese nationality (n=20), late report of emigration occurring before the start of follow-up (n=117), incorrect birth date (n=5) or duplicate registration (n=2). Thus, a population-based cohort of 67,376 women from the JPHC Study were identified as eligible to be included in the present report, 27,377 from cohort I, and 39,999 from cohort II. Of these, 55,840 women [83%; 22,469 (82%) in cohort I and 33,371 (83%) in cohort II] returned the JPHC Study questionnaire, which contained questions on menstrual and reproductive history, use of exogenous hormones (defined as use of any exogenous hormone, including oral contraceptives or HRT), body size (height in cm, and weight in kg at baseline), smoking habits (including second-hand smoke), alcohol consumption, physical activity during leisure time, usual sleep duration and family history of cancer in a first-degree relative, among others.

Of the 55,840 women who completed the questionnaire, we excluded from all analyses presented in this article 1,455 women who had a history of cancer at baseline, 8,637 with missing data at enrollment for any of the main exposure variables under study except for alcohol, and 1,340 women due to too many missing values. We further excluded all women who reported artificial menopause before cohort enrollment (~10% of the cohort), as there was a possibility that they had been hysterectomized and/or oophorectomized, and therefore not at risk for epithelial ovarian cancer. Information on hysterectomy and oophorectomy was not available. This left a total of 45,748 women who were followed up.

Study participants were informed in writing about the objectives and methods of the JPHC Study and those who responded to the questionnaire were regarded as consenting to participate in the study. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Follow-up and identification of cancer cases. Person-years of follow-up were calculated from the date of return of the baseline questionnaire until the date of diagnosis of epithelial ovarian cancer, relocation from the study area (i.e., migration), death, or end of the study period (December 31, 2008), whichever occurred first. Data on residential relocation were obtained from residential registries. Among the 45,748 study subjects followed up, 3,046 died, 4,290 moved and 190 were lost to follow-up. Death certificates, coded according to the requirements of the Ministry of Health, Labor and Welfare, were collected through local public health centers with permission. Incidence data for cancer were collected though two data sources, major local hospitals and population-based cancer registries. Death certificates were used to supplement the information on cancer incidence. Cancer incidence data were only collected for subjects living in the study areas. Members of the JPHC Study Group coded the tumor site of origin and histological subtype using the International Classification of Diseases for Oncology, 3rd edition. Epithelial ovarian cancer cases were defined as women with an incident cancer with the following codes: C56-9, histologies 8000, 8041, 8120, 8140, 8260, 8310, 8323, 8380, 8440, 8441, 8450, 8460, 8470, 8471 and 8480. Non-epithelial tumors, namely carcinosarcomas (C56-9, histology 8980, n=3), dysgerminomas (C56-9, histology 9060, n=1) and teratomas (C56-9, histology 9080, n=2) were excluded from the analysis, as their risk factors may differ from those for epithelial ovarian cancer (26), and the small number of cases in our cohort would have precluded meaningful conclusions. All other histological subtypes were combined in the analyses, as we did not have enough cases to perform separate analyses for each histological subtype. Borderline ovarian tumors are not recorded by the cancer registration system in Japan, and therefore were not included in this study.

Statistical analysis. The stratified Cox proportional hazard model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) estimating the relative risk of epithelial ovarian cancer according to the exposures under study. HRs and 95% CIs for continuous variables are reported with two decimal digits, while all others are reported with one decimal digit only. Attained age with delayed entry was used as a time scale (27) in the model. Treating the study areas as a stratifying variable (28) allowed for different baseline hazards in the different study areas. The assumption of the proportional hazards in the Cox model was checked and found to be satisfactory (28).

We performed analyses based on the following variables: age at menarche (<14, 14, 15, >15 years, and as a continuous variable per 1-year increase), parity (nulliparous versus parous, and 0, 1, 2, 3, >3 births, and as a continuous variable per additional birth), age at first birth among parous women (<22, 22-25, 26-29, >29 years, and as a continuous variable per 1-year increase), history of breastfeeding among parous women (no, yes) use of exogenous hormones (no, yes; please note that as only information on any hormone use was available, it was not possible to separate use of oral contraceptives or HRT), menopausal status at enrollment (premenopausal, postmenopausal with natural menopause), height (in cm, and as a continuous variable per 10 cm increase), body mass index (BMI, calculated as weight in kg at baseline divided by height in m^2; the self-reported height and weight data were validated (29) and then categorized: <18.5, 18.5-19.9, 20-22.9, 23-24.9, 25-29.9, >29.9, and as a continuous variable per BMI unit increase), smoking status (never or ever smoker), exposure to second-hand smoke (no, yes), alcohol consumption (no, yes, and as a continuous variable in grams per week), physical activity during leisure time (no, yes), usual sleep duration (<6, 6-7, >7 h per day, and as a continuous variable per hour), and family history of cancer in a first-degree relative (i.e., mother, father, siblings; no, yes). Cut-points for categorization of each variable were decided based both on the hypothesized

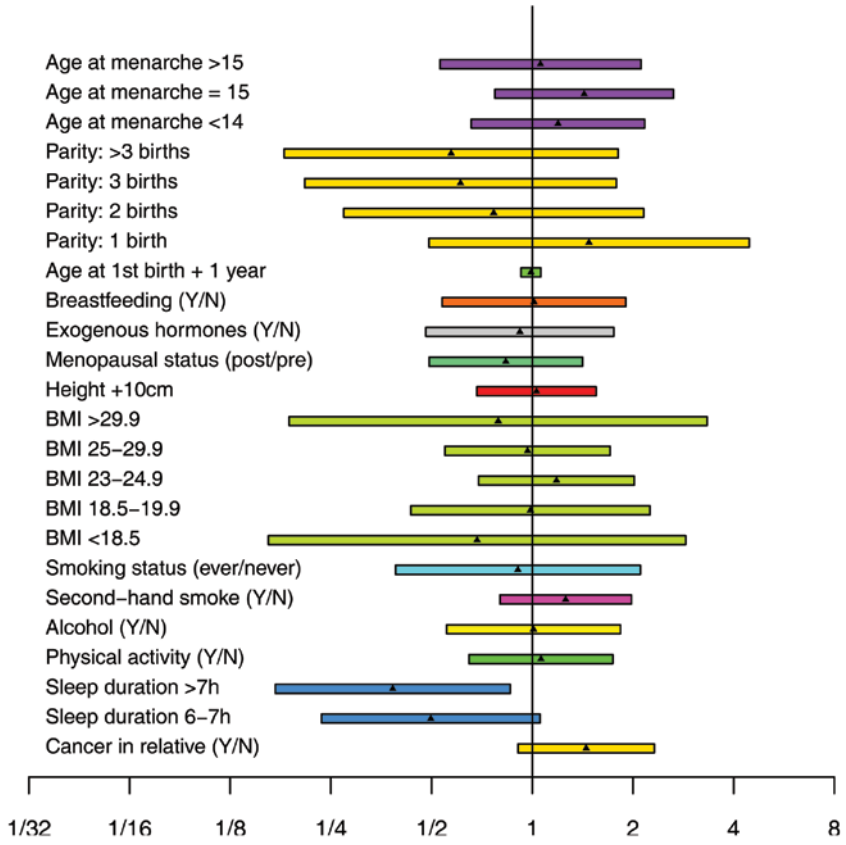

Figure 1. Hazard ratios (black triangles) and two-sided 95% confidence intervals (horizontal boxes) of epithelial ovarian cancer according to selected menstrual and reproductive factors, anthropometric characteristics, and lifestyle factors. The Japan Public Health Center-based Prospective Study. Abbreviations: BMI, body mass index; Y, yes; N, no. NOTE: Estimates correspond to Table II. Reference categories are: age at menarche, 14 years; parity, 0; breastfeeding, no; exogenous hormones, no; menopausal status, premenopausal; BMI, 20-22.9; smoking status, never; second-hand smoke, no; alcohol, no; physical activity, no; sleep duration, <6 h; cancer in relative, no.

biological effects on epithelial ovarian cancer risk, as well as on the frequency distribution of the variables within the cohort (17,29-31).

We fitted basic models, further stratifying by study area and using attained age as a time scale. We also fitted multivariable models including all variables as described above simultaneously. To ensure that comparisons between models and covariables were not dependent on missing values, all models were fitted to a dataset with complete data for all the primary covariables of interest. In a supplementary set of analyses, one restricted to parous women and another to women answering the question on alcohol consumption, we also re-fitted the models on datasets using all available data for each model. Second-hand smoke was analyzed among all women, regardless of their smoking status, and subsequently restricted to never smokers.

All p-values reported are two-sided, and the significance level was set at $p<0.05$. For data management and for summary statistics and graphs the SAS software version 9.2 was used. Cox models were fitted using the survival package in the R software version 2.9.2 running Linux Debian.

Results

Baseline characteristics of the study population are shown in Table I. The 45,748 women included our analyses were followed up for a median of 16 years. During follow-up, only 86 newly arising cases of epithelial ovarian cancer were recorded: 35 serous adenocarcinomas (histologies 8140, 8260, 8441, 8450, 8460), 16 clear-cell adenocarcinomas (histology 8310), 13 mucinous adenocarcinomas (histologies 8470, 8471, 8480), six endometrioid adenocarcinomas (histology 8380), three other adenocarcinomas (small cell adenocarcinoma, histology 8041; transitional adenocarcinoma, histology 8120; other, histology 8323), and 13 adenocarcinomas not otherwise specified (histology 8000). The overall age-standardized incidence rate (SIR) of ovarian cancer in the cohort was 11 per 100,000 women.

The median age at diagnosis was 59 years, with a median follow-up before diagnosis of 7.6 years. There were no differences between the mean ages at enrollment, menarche, or first birth, nor between BMI and usual sleep duration between women with and without epithelial ovarian cancer. The proportions of women who were nulliparous, had never breastfed (among parous women), had used exogenous hormones, were premenopausal at enrollment, and who reported smoking, being exposed to second-hand smoke, consuming alcohol, and being physically active during leisure time were also similar between women who did and did not develop epithelial ovarian cancer during follow-up. The proportion of women with a history of cancer in a first-degree relative was 30.2% among women with, and 22.7% among women without epithelial ovarian cancer (Table I).

Table I. Characteristics of study participants (n=45,748) at baseline.[a]

Characteristics	Women		Epithelial ovarian cancer cases		Non-cases	
	Number	%	Number	%	Number	%
Number of participants	45,748	100	86	0.2	45,662	99.8
Age at enrollment, years						
40-49	19,501	42.6	34	39.5	19,467	42.6
50-59	18,848	41.2	42	48.8	18,806	41.2
60-69	7,399	16.2	10	11.6	7,389	16.2
Age at menarche, years						
<14	13,203	28.9	26	30.2	13,177	28.9
14	11,208	24.5	19	22.1	11,189	24.5
15	9,565	20.9	23	26.7	9,542	20.9
>15	11,772	25.7	18	20.9	11,754	25.7
Parity						
Nulliparous	2,904	6.4	6	7.0	2,898	6.3
1	3,421	7.5	12	14.0	3,409	7.5
2	16,231	35.5	34	39.5	16,197	35.5
3	12,915	28.2	21	24.4	12,894	28.2
>3	10,277	22.5	13	15.1	10,264	22.5
Parous, number of births	42,844	93.6	80	93.0	42,764	93.6
Age at first birth among 42,844 parous women, years						
<22	6,103	14.2	9	11.2	6,094	14.2
22-25	20,975	49.0	41	51.2	20,934	49.0
26-29	11,982	28.0	20	25.0	11,962	28.0
>29	3,784	8.8	10	12.5	3,774	8.8
Breastfeeding among 42,844 parous women						
Nulliparous/never	2,904	6.3	6	7.0	2,898	6.3
No	5,413	11.8	12	14.0	5,401	11.8
Yes	37,431	81.8	68	79.0	37,363	81.8
Use of exogenous hormones						
No	39,927	87.3	75	87.2	39,852	87.3
Yes	5,821	12.7	11	12.8	5,810	12.7
Menopausal status at enrollment[b]						
Premenopausal	19,815	43.3	40	46.5	19,775	43.3
Postmenopausal (natural)	25,933	56.7	46	53.5	25,887	56.7
Body mass index, kg/m^2						
<18.5	1,654	3.6	2	2.3	1,652	3.6
18.5-19.9	3,900	8.5	7	8.1	3,893	8.5
20-22.9	16,667	36.4	31	36.0	16,636	36.4
23-24.9	10,793	23.6	24	27.9	10,769	23.6
(20-24.9)	27,460	60.0	55	64.0	27,405	60.0
25-29.9	11,302	24.7	20	23.3	11,282	24.7
>29.9	1,432	3.1	2	2.3	1,430	3.1
Smoking status						
Never	41,957	91.7	80	93.0	41,877	91.7
Ever	3,791	8.3	6	7.0	3,785	8.3
Exposure to second-hand smoke among all women						
No	29,479	64.4	49	57.0	29,430	64.4
Yes	16,269	35.6	37	43.0	16,232	35.6

Table I. Continued.

Characteristics	Women		Epithelial ovarian cancer cases		Non-cases	
	Number	%	Number	%	Number	%
Exposure to second-hand smoke among 41,957 never smokers						
No	27,852	66.4	47	58.8	27,805	66.4
Yes	14,105	33.6	33	41.2	14,072	33.6
Alcohol consumption among 44,408 women[c]						
No	36,707	82.7	68	82.9	36,639	82.7
Yes	7,701	17.3	14	17.1	7,689	17.3
Physical activity during leisure time						
No	34,066	74.5	64	74.4	34,002	74.5
Yes	11,682	25.5	22	25.6	11,660	25.5
Usual sleep duration, h						
<6	2,419	5.3	8	9.3	2,411	5.3
6-7	27,085	59.2	53	61.6	27,032	59.2
>7	16,244	35.5	25	29.1	16,219	35.5
Family history of cancer in a first-degree relative						
No	35,337	77.2	60	69.8	35,277	77.3
Yes	10,411	22.8	26	30.2	10,385	22.7
Mean and SD	Mean	SD	Mean	SD	Mean	SD
Age at enrollment, years	51	7.9	51	7.5	51	7.9
Age at menarche, years	15	1.9	14	1.7	15	1.9
Age at first birth among 42,844 parous women, years	25	3.5	25	3.6	25	3.5
Height, cm	152	5.6	152	5.4	152	5.6
Body mass index, kg/m^2	23	3.2	23	2.6	23	3.2
Alcohol consumption, g/week	17	89.2	12	53.1	17	89.2
Usual sleep duration, h	7	1	7	1	7	1

[a]The Japan Public Health Center-based Prospective Study. [b]Women who reported artificial menopause were excluded from the cohort, as the cause (which could have been oophorectomy) was unknown. [c]Includes women answering the question on alcohol. SD, standard deviation.

The HRs and 95% CIs of epithelial ovarian cancer according to potential risk factors are shown in Table II, and displayed graphically in Fig. 1. Overall, there were no statistically significant associations for age at menarche, age at first birth, breastfeeding, use of exogenous hormones, menopausal status at cohort enrollment, height (multivariable HR per 10 cm increase = 1.03, 95% CI 0.68-1.55), BMI (multivariable HR per BMI unit increase = 1.00, 95% CI 0.94-1.08), smoking, exposure to second-hand smoke, alcohol consumption, physical activity during leisure time and family history of cancer in a first-degree relative (multivariable HR=1.4, 95% CI 0.9-2.3) (Table II, Fig. 1). The decrease in HR associated with each additional birth was 0.75 (95% CI 0.56-0.99). In both the age- and study area-adjusted model, as well as in the multivariable model there was evidence of an inverse association with usual sleep duration. Women who usually slept more than 7 h per day had an HR of 0.4 (95% CI 0.2-0.9) compared to those who usually slept less than 6 h; results were similar in the model adjusted for age and study area, and in the multivariable model (Table II, Fig. 1). The results described above and presented in Table II remained basically unchanged when we restricted the analyses to parous women, when we included women who reported artificial menopause (data not shown), when we excluded the variable use of exogenous hormones from the multivariate models, and when we used covariables in a continuous format instead of as categorical variables (for age at menarche, parity, age at first birth among parous women, height, BMI, alcohol consumption and usual sleep duration). Results of the supplementary set of analyses, where we re-fit models on datasets using all available data for each model

Table II. Hazard ratios (HR) and 95% confidence intervals (CI) of epithelial ovarian cancer according to menstrual and reproductive factors, anthropometric characteristics, and lifestyle factors among study participants (n=45,748).[a]

Characteristics	Age and study area adjusted		Multivariable adjustment	
	HR[b]	95% CI	HR[c]	95% CI
Age at menarche, years				
<14	1.2	0.7-2.2	1.2	0.7-2.2
14	1.0 (ref)		1.0 (ref)	
15	1.4	0.8-2.6	1.4	0.8-2.6
>15	1.0	0.5-2.0	1.1	0.5-2.1
Per 1-year increase (continuous variable)	0.95	0.83-1.09	0.97	0.84-1.10
Nulliparous				
No	1.0 (ref)		1.0 (ref)	
Yes	1.3	0.6-3.0	1.3	0.6-3.1
Parity, number of births				
0	1.0 (ref)		1.0 (ref)	
1	1.5	0.6-4.0	1.5	0.5-4.5
2	0.8	0.3-1.9	0.8	0.3-2.1
3	0.6	0.3-1.6	0.6	0.2-1.8
>3	0.6	0.2-1.6	0.6	0.2-1.8
Per additional birth (continuous variable)	0.81	0.67-0.99	0.75	0.56-0.99
Age at first birth among 42,844 parous women, years				
<22	0.8	0.4-1.6	0.8	0.4-1.8
22-25	1.0 (ref)		1.0 (ref)	
26-29	0.9	0.5-1.6	0.9	0.3-2.3
>29	1.6	0.8-3.2	1.2	0.6-2.6
Per 1-year increase (continuous variable)	1.02	0.96-1.09	0.99	0.92-1.06
Breastfeeding among 42,844parous women				
No	1.0 (ref)		1.0 (ref)	
Yes	0.9	0.5-1.7	1.0	0.5-1.9
Use of exogenous hormones				
No	1.0 (ref)		1.0 (ref)	
Yes	0.9	0.5-1.8	0.9	0.5-1.7
Menopausal status at enrollment				
Premenopausal	1.0 (ref)		1.0 (ref)	
Postmenopausal (natural)	0.8	0.5-1.4	0.8	0.5-1.4
Height, per 10 cm increase (continuous variable)	1.06	0.71-1.57	1.03	0.68-1.55
Body mass index, kg/m^2 at enrollment				
<18.5	0.7	0.2-3.0	0.7	0.2-2.9
18.5-19.9	1.0	0.5-2.3	1.0	0.4-2.2
20-22.9	1.0 (ref)		1.0 (ref)	
23-24.9	1.2	0.7-2.0	1.2	0.7-2.0
25-29.9	0.9	0.6-1.7	1.0	0.5-1.7
>29.9	0.8	0.2-3.3	0.8	0.2-3.3
Per BMI unit increase (continuous variable)	1.00	0.93-1.07	1.00	0.94-1.08
Smoking status				
Never	1.0 (ref)		1.0 (ref)	
Ever	1.0	0.4-2.3	0.9	0.4-2.1
Exposure to second-hand smoke among 41,957 never smokers				
No	1.0 (ref)		1.0 (ref)	
Yes	1.3	0.8-2.1	1.3	0.8-2.0

Table II. Continued.

Characteristics	Age and study area adjusted		Multivariable adjustment	
	HR[b]	95% CI	HR[c]	95% CI
Alcohol consumption among 44,408[d]				
No	1.0 (ref)			
Yes	1.0	0.6-1.8	1.0	0.5-1.8
Grams/week (continuous variable)	1.00	0.99-1.00	1.00	0.99-1.00
Physical activity during leisure time				
No	1.0 (ref)		1.0 (ref)	
Yes	1.1	0.7-1.8	1.1	0.6-1.7
Usual sleep duration, h/day				
<6	1.0 (ref)		1.0 (ref)	
6-7	0.5	0.2-1.1	0.5	0.2-1.0
>7	0.4	0.2-0.9	0.4	0.2-0.9
Per hour (continuous variable)	0.80	0.65-0.99	0.80	0.65-0.99
Family history of cancer in first-degree relative				
No	1.0 (ref)		1.0 (ref)	
Yes	1.5	0.9-2.3	1.4	0.9-2.3

[a]The Japan Public Health Center-based Prospective Study. [b]Adjusted for age and study center. [c]Adjusted for the other variables in the table except for alcohol. [d]Women answering the question on alcohol were analyzed separately in a model with all other variables included.

(i.e., not excluding missing values from all covariables) were no different than the results of the main models presented in Table II (data not shown).

Discussion

In this population-based prospective cohort of Japanese women, we found an inverse association between parity and usual sleep duration of more than 7 h and epithelial ovarian cancer risk. We did not observe any clear associations with other reproductive or menstrual characteristics, body size, or lifestyle characteristics, such as use of exogenous hormones, smoking status, exposure to second-hand smoke, alcohol consumption and physical activity during leisure time. There was an indication of a weak positive association between family history of cancer in a first-degree relative and epithelial ovarian cancer risk.

The present study has some advantages. The prospective study design potentially avoids selection bias and recall bias, and the relatively high response rate (>80%) and very low rate of loss to follow-up indicate that our results well reflect the epithelial ovarian cancer risk profile in the Japanese female population. It is the largest prospective population-based cohort study conducted in Japan to-date that is able to examine risk factors for epithelial ovarian cancer in detail. Nonetheless, the number of incident epithelial ovarian cancer cases in the cohort is limited, due to the relatively low overall incidence of ovarian cancer in both the Japanese population in recent years (SIR 8 per 100,000 women) (1), and in the cohort itself (SIR 11 per 100,000 women). As a result, this study had restricted statistical power in order to detect possible weak associations, which were expected based on information from previously published studies. Moreover, we could not perform stratified analyses by histological subtypes of epithelial ovarian cancer due to lack of statistical power for subgroup analysis.

Information on hysterectomy and oophorectomy was not available for the cohort, and we excluded women who reported artificial menopause at cohort enrollment from all analyses, as the cause (which could have been hysterectomy or oophorectomy) was unknown. Nevertheless, our sensitivity analyses, which did include women who reported artificial menopause before cohort enrollment, yielded results that were similar to those in the analyses excluding them. Finally, several variables had a substantial amount of missing values, and we handled this problem by performing the analysis twice, with and without the inclusion of women and variables with missing values, with virtually identical results.

In our study there was an inverse association between epithelial ovarian cancer risk and increasing number of births (multivariable HR=0.75, 95% CI 0.56-0.99). Studies carried out elsewhere (9), as well as a few case-control studies in Japan (8,20,23,25) have reported similar inverse associations.

Previous studies, mainly from Western countries, have indicated an association between nulliparity, and, less consistently, early age at menarche, delayed age at first birth, never breastfeeding, and ovarian cancer risk (9). In addition, one case-control study in Japan reported a decrease in ovarian cancer risk with older age at menarche (25). However, we could not confirm these findings; none of these associations were statistically significant in our study. This could be due to a different epithelial ovarian cancer risk profile among Japanese women compared to women in North America and Europe, where most previous studies were performed. Indeed, the mean age

at menarche in our cohort was higher than among Caucasians. Alternatively, it could be explained by the limited statistical power we used in order to detect relatively weak associations.

In our study no associations were observed between exogenous hormone use and epithelial ovarian cancer risk. The International Agency for Research on Cancer (IARC) recently evaluated the evidence on the carcinogenicity of pharmaceuticals to humans, and concluded that use of combined estrogen-progestin oral contraceptives decreases ovarian cancer risk, while estrogen-only HRT increases risk (10). In our study the information on use of exogenous hormones was collected as a single variable, grouping together oral contraceptives and HRT, which is an important limitation. Thus the fact that we did not find any effect is not surprising, as the opposite effects of oral contraceptives and HRT could in theory cancel each other out. Results from a sensitivity analysis removing this variable entirely from the multivariate models did not substantially alter risk estimates for the other variables analyzed. Moreover, reported exogenous hormone use in our study was most likely due to oral contraceptive use, as HRT use in Japan is extremely low. Indeed, HRT use was reported by only 12% of our study population, among women with and without epithelial ovarian cancer alike, and the duration of use was usually extremely short (>1 year for the entire cohort and for women with epithelial ovarian cancer). This proportion of women and short length of use is far lower than those reported in studies from the United States and Western Europe, from where most of the evidence on associations between exogenous hormones and ovarian cancer emanates. Previous case-control studies in Japan reported either an inverse association between ovarian cancer risk and oral contraceptive use (18,23), or no association (20,25).

Menopausal status at cohort enrollment was not associated with epithelial ovarian cancer risk in our study. Also there was no statistically significant association between height and epithelial ovarian cancer risk. According to the World Cancer Research Fund (WCRF), adult attained height probably increases ovarian cancer risk. Although it is considered that height *per se* is unlikely to directly modify cancer risk, it may be a marker for genetic, environmental, hormonal and nutritional factors affecting growth from preconception to completion of linear growth (13). The evidence on which the WCRF based its evaluation emanated from 12 studies: nine in Western populations and three in Asian populations. Among the studies in Asian populations, two were case-control studies from Japan, both of which found a non-statistically significant increase in relative risk per 10 cm increase in height: Mori *et al* (8) reported an odds ratio (OR) of 1.11 (0.67-1.88) and Hirose *et al* (24) an OR of 1.12 (0.67-1.88), and one case-control study in China reported an OR of 1.26 (0.88-1.80) (32). Again, the mean stature of women in our study was lower than in other studies, including those on which the WCRF based its conclusions. We found no clear association between BMI and epithelial ovarian cancer risk in our study; the WCRF concluded that there was limited evidence, and that no conclusion could be reached about any relationship between body fatness, abdominal fatness, weight change, or energy intake (which we could not evaluate in our study) and ovarian cancer risk (13). The mean BMI in our cohort was also lower than in the studies included in the WCRF evaluation. One previous Japanese cohort study (14) and three Japanese case-control studies (8,23,24) reported a positive association between increasing BMI and risk for epithelial ovarian cancer, although the results were not entirely consistent.

The prevalence of smoking in our cohort was very low, and there was no evidence of an association with epithelial ovarian cancer risk. As most of the women who had ever smoked in our cohort were former smokers, we did not perform separate analyses for current smokers, as our statistical power was too low to reach any conclusions. Although most studies in Western populations have not indicated an association between smoking and ovarian cancer risk, some recent studies, including cohort studies, have reported a positive association between smoking and risk of mucinous ovarian cancer (12). A recent comprehensive review of the worldwide scientific literature on the carcinogenicity of tobacco smoke (12) concluded that there was sufficient evidence to classify cigarette smoking as carcinogenic in relation to mucinous ovarian cancer, but not in relation to other histological subtypes. One previous cohort study in Japan reported a positive association between current smokers of 10-19 cigarettes per day, compared to never smokers, and ovarian cancer risk (15).

Exposure to second-hand smoke was over 30% among women in our cohort, most probably reflecting the high prevalence of smoking among Japanese men. We found no association between exposure to second-hand smoke and risk of epithelial ovarian cancer in our study, in agreement with the scientific literature (12). There were an insufficient number of studies on exposure to second-hand smoke and epithelial ovarian cancer risk in the scientific literature to allow the IARC to draw conclusions about any possible association (12). We could not identify in the literature any previous study about second-hand smoke and ovarian cancer risk in Japan.

Alcohol consumption was not positively associated with epithelial ovarian cancer risk in our cohort, in agreement with most of the scientific literature (12), save one Japanese case-control study which reported an inverse association (21). Detailed analysis by type of beverage (beer, sake, etc.) was not possible in our cohort due to small numbers, although there is no evidence in the scientific literature suggesting that we should expect a different effect on ovarian cancer risk by type of alcoholic beverage (12).

Physical activity during leisure time was not associated with epithelial ovarian cancer risk in our study. Similarly, the WCRF concluded that there is limited evidence and no conclusions can be drawn based on the published scientific literature on a possible association between physical activity during leisure time and ovarian cancer risk (13).

Our findings of an association between usual sleep duration and epithelial ovarian cancer risk are novel, as we could not identify prospective cohort studies describing such an association previously. We cannot entirely rule out the possibility that this is a chance finding. However, if studies in other populations could confirm these results, this finding may be of public health significance in cancer prevention. A protective effect of usual sleep duration has been suggested for other cancer sites, as well as for cardiovascular diseases (33,34). Mechanisms underlying the suggested association between usual sleep duration and epithelial ovarian cancer risk may include the melatonin pathway (33). Light exposure during biological darkness and

the associated circadian disruption seem to affect cancer incidence and growth in the majority of studies (46 out of 56 studies) in animal models, which were evaluated recently by the IARC (33). For ovarian cancer in particular, studies in animal models indicated that pinealectomized hamsters that were inoculated subcutaneously with ovarian tumor cells had an ovarian tumor volume that was about five-fold greater than control hamsters with intact pineal glands (35). Pinealectomy suppresses the physiological nocturnal melatonin signal leading to the enhancement of cancer development and/or growth in animal models. At the same time, this procedure indirectly raises the question of whether the physiological nocturnal melatonin signal from the pineal gland inhibits the process of tumorigenesis in animal models (33).

Family history of cancer in a first-degree relative was not statistically significantly associated with epithelial ovarian cancer risk in our study, as has been reported in studies elsewhere (9), and in a few Japanese case-control studies (8,20,23). However, the HR point estimate indicated a weak increase in epithelial ovarian cancer risk among women with a family history of cancer in a first-degree relative. The number of cases in our study was too limited to perform analyses by cancer type in the relatives, which would be desirable. Further follow-up of the cohort is needed for these types of detailed analyses.

In conclusion, in this prospective cohort study on epithelial ovarian cancer in Japanese women, parity and usual sleep duration of more than 7 h per day were both associated with a decrease in risk. Other risk factors that were reported to be associated with epithelial ovarian cancer in several studies in Western countries (9), a few Japanese case-control studies (8,18-20,23-25), and one Japanese cohort study (14,15), such as age at menarche, age at first birth, breastfeeding, use of exogenous hormones, height, BMI and physical activity, were not observed in this study in Japan. Family history of ovarian cancer was positively associated with the HR point estimate (although not significantly), in agreement with studies among Western women and a few Japanese case-control studies (8,20,23), although the association in our study was not statistically significant. Smoking or exposure to second-hand smoke, as well as alcohol consumption, were not associated with epithelial ovarian cancer risk in our study, which was also the case in most studies among Western women. Previous prospective cohort studies in Japan indicated a possible association with smoking (15) and BMI (14), although it was not statistically significant. Overall, the previous Japanese case-control studies presented mixed results regarding different risk factors for ovarian cancer (8,18-25).

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