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Ovarian cancer mortality among women aged 40–79 years in relation to reproductive factors and body mass index: latest evidence from the Japan Collaborative Cohort study

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Objective: This study mainly aimed to investigate the association of ovarian cancer mortality with reproductive factors and body mass index among Japanese women aged 40–79 years.

Methods: The source of the data was the Japan Collaborative Cohort (JACC) study which covered the period of 1988 to 2009. A representative sample of 64,185 women was used. Cox model was used to estimate the relative risk (RR) and 95% confidence interval (CI).

Results: The total number of ovarian cancer deaths was 98, with a mortality rate of 9.30 per 100,000 person-years. Women with single marital status revealed significantly higher age-adjusted RR (RR, 4.11; 95% CI, 1.66 to 10.23; p=0.005) as compared to married women. The effect of single marital status was stronger among older women aged 50+ years (RR, 4.58; 95% CI, 1.65 to 12.72; p=0.003) than younger women. An elevated risk was found for both nulliparous and nullipregnant women. Similarly, an increased risk of ovarian cancer mortality was estimated among overweight among aged 50 years or less.

Conclusion: Out of many factors only single marital status indicated a higher risk for ovarian cancer mortality. All other factors provided inconclusive results, which imply further epidemiological investigations.

Keywords: Japan, Marital status, Ovarian cancer, Prospective cohort study, Reproductive history

INTRODUCTION

Globally overall cancer burden including the burden of ovarian cancer (OC) is increasing. The OC is the sixth and eighth leading cause of cancer mortality among women in developed and developing countries [1]. The worldwide estimated number of new OC cases increased from 137,600 in 1980 [2] to 225,000 in 2008 [1]. This gynecologic cancer mainly results from the malignant transformation of the ovarian surface epithelium [3], which approximately accounts for 90% of the total OC and generally develops after the age of 40 years [4].

As compared to the European and other developed countries, the OC is less dominant in Japan [5,6]. However, an increasing trend of OC has been observed in this country since 1975 [5-8]. For example, the age-standardized incidence of OC per 100,000 women increased from 6.4 in 2002 to 7.6 in 2008 in Japan [6,8]. The crude incidence rate per 100,000 women increased from 4.2 to 8.4 during the period of 1975–1998, whereas the age-standardized incidence rate increased from 4.0 to 5.4 per 100,000 women during the same period [7]. Several factors

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such as increased notification of OC from the concerned authorities and institutions due to better diagnostic facilities, changing dietary patterns and adoption of westernised lifestyles may contribute to the rising trend of OC [1,9].

Risk or protective factors for OC can broadly be grouped as socio-demographic (e.g., age, race, marital status) [10,11]; reproductive (e.g., number of pregnancy, parity, age at first birth, age at menarche) [10-14]; family history of cancer [14-17]; past history of diabetes [17]; dietary habits [17]; anthropometric measures (height, overweight/obesity) [14,17,18]; menopausal status and use of hormonal drugs [13,14,19-21]; use of oral contraceptives [11-13]; lifestyle factors such as smoking [5,22,23], drinking [14,22,24-26], physical activity [14,22,27-29], and walking [28].

Smoking is reported as a risk [5,23], protective [22] or independent factor for OC [14]. Similarly, alcohol drinking revealed increased [24], decreased [25] and no risk for OC [14,22,26]. Inconsistencies are also seen for other lifestyle factors (e.g., physical activity), anthropometric measures, a family history of cancer, dietary habits, menopausal status and hormonal use. These inconsistencies may arise from the variation of the study design, sample size and settings of the study. Most of the studies used a case-control design, which may suffer from recall and selection bias. Only few studies used cohort design. Moreover, interpretations of results are hampered by inadequate control for potential confounding factors, small sample sizes, and differences in reference groups [13]. All these inconsistencies underscore the necessities of further epidemiological studies based on a large sample of a cohort study.

Our study is an important attempt in this regard. Here we report the association of OC with various factors except dietary habits and use of oral contraceptives. However, attentions were given only to those factors which showed an elevated risk of mortality in the age-adjusted Cox model. We utilised the final data (ended in 2009) of the Japan Collaborative Cohort (JACC) study, which is one of the biggest prospective cohort studies for evaluating the cancer risk in Japan. Briefly, some characteristics of this study such as the long follow-up period and generation of reliable data made it unique in Japan. As the selected characteristics of study participants were similar to those of the Japanese general population, this study could also be regarded as a representative study of the Japanese population [30].

MATERIALS AND METHODS

Relevant data for this article were extracted from the JACC study, which was established in the late 1980s to evaluate the risk impact of lifestyle factors and levels of serum components on human health. The Ethical Board at Nagoya University School of Medicine approved this study. As this study is a prospective cohort study for all cancer sites, the study protocol included potential risk factors not only for OC but also for other cancers. The detailed information concerning the study design was explained elsewhere [31,32]. Briefly, the JACC study is a multicenter-collaborative study in which 24 institutions participated voluntarily. Study subjects were recruited from 45 areas of Japan except Shikoku district. Baseline data was mostly collected from 1988 to 1990 [30]. Individual informed consent prior to participation in the study was obtained in 36 of the 45 study areas (written consent in 35 areas and oral consent in 1 area), while in the remaining 9 areas, group consent from the head of the area was obtained. The JACC study recruited an initial sample of 110,585 respondents (men, 46,398; women, 64,190) aged 40–79 years. In order to extract the final sample for the present study, several exclusion criteria were applied. First, we excluded all the male subjects as we only focused on OC mortality related to women. Later, we excluded all females who had a history of OC (International Classification of Diseases [ICD] 9, 183) at the time of baseline survey. Finally, we got a sample of 64,185 women for detailed analyses.

1. Follow-up

The whole study including the follow-up period in most areas was ended at the end of 2009 [30]. In some areas the follow-up was ended even early: at the end of 1999 (4 areas), 2003 (4 areas) and 2008 (2 areas). The main reason for different follow-up periods was the retirement of major researchers in different years from their study areas. During the follow-up period, statuses of subjects (namely deaths, lost-to follow-up, and alive) were ascertained annually or biannually by the investigators. The investigators reviewed the population registry of cohort members to determine the causes of deaths with the permission of the director-general of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post and Telecommunications) and/or the Ministry of Health, Labor and Welfare, Japan. The date of move-out of cohort members from the study areas were also annually or biannually verified by the investigator in cooperation with key members of the local governmental office [33]. For the present study, the event of interest was the survival time from enrollment to death due to OC. Here censored cases meant all (1) drop/move out cases during follow-up, (2) deaths except OC death, and (3) cases who survived until the end of the follow-up. It should be noted that this article utilised only a part of the whole study findings. Many articles have already been published on differ-

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ent cancers [30] including OC [5,33,34] since the inception of the JACC study.

2. Baseline information

A lot of information at baseline survey e.g., demographic information; schooling; past history of 7 acute infectious and 11 chronic diseases; health check-up including screening; lifestyles (e.g., smoking, alcohol drinking and physical activity); anthropometric measures; reproductive history; food habits and blood samples (partly) were collected using self-administered questionnaire. However, only few of them were considered for analyses.

3. Adjusted variables

Some of the evaluated factors used as adjusted variables in the Cox model are listed in Table 1. The composite variable for family history of cancer was based on the histories of various cancers either in father or mother or siblings, which included breast (ICD9, 174), endometrial (ICD9, 182) and ovarian (ICD9, 183) cancers for mother and sister, and prostate cancer (ICD9, 185) for father and brother.

It should be noted that the accessibility to screening program for cancer in Japan is fairly good. However, there is no national screening programme which is directly provided by the Japanese Government. Only several screening programs for cancer are indirectly supported by the government. Moreover, insurance does not cover screening programs [35,36].

4. Target variables

Several reproductive variables namely marital status (married, widowed, divorced, single), age at marriage in years (11–19, 20–25, 26+), number of pregnancy (0, 1–2, 3–4, 5+), number of live birth (0, 1–2, 3–4, 5+), age at first delivery in years (11–22, 23–26, 27+), age at menarche in years (below 14, 15–16, 17+), age at menopause in years (<50, 50+), and history of hormonal drug use (yes, no) including body mass index (BMI; underweight, normal, overweight) were considered as target variables.

5. Statistical analyses

All statistical analyses were performed using IBM SPSS ver. 19.0 (IBM Inc., Armonk, NY, USA). Firstly, we presented the distribution of women, OC deaths, person-years (PYs) and death rate per 100,000 PYs for each category of the adjusted and target variables (Tables 1, 2). Using Cox-proportional hazard model, we estimated the age-adjusted (model I) and multivariable-adjusted (model II) relative risk (RR) and 95% confidence interval (95% CI) for all target variables (Table 2). Before entering target and adjusted variables into the multivariable model, we checked the multicollinearity using variance inflation factor (VIF) statistic. None of the variables suffered from the multicollinearity as all VIFs were less than 3. We also checked the interaction effect of marital status, pregnancy and delivery on OC death, which was highly insignificant. Therefore, we did not report this finding. Lastly, we calculated age-adjusted (continuous) RR and 95% CI for two mutually exclusive groups of women using the cut-off age of 50 at baseline (Table 3). We excluded all women with single marital status while analyzing three variables namely age at marriage, number of pregnancy and number of live birth. We used this exclusion criterion, as more than 90% of the women were nullipregnant or nulliparous. Similarly, all nulliparous women were excluded from the variable age at first delivery. Any result with a p-value of 0.05 was considered as statistically significant.

RESULTS

1. Descriptive characteristics

The total number of OC deaths was 98 during the average follow-up period of 16.41 PYs. The mortality rate was 9.30 per 100,000 PYs. The average age of women at baseline survey was about 58 years with a standard deviation of 10.1 years. According to Table 1, the highest percentage of women was non-smoker (92.7%) and non-drinker (73.9%). A majority of women belonged to the category of normal BMI (70.9%), followed by overweight (22.8%) and underweight (6.4%), respectively.

According to Table 2, slightly over 80% of the women (82.4%) were married and only few of them were single. Most of the married women (83.8%) got married between 20 to 25 years of age with an average of 23.4 years. The average number of pregnancy per woman was 3.4, with the highest percentage in the category of 3 to 4 children, followed by the category of 1 to 2 children. Only few women reported no pregnancy. In contrast, the average number of live births was 2.7 per woman, with the highest percentage in the group of 1 to 2 births, followed by the group of 3 to 4 births. The average age of first delivery for parous women was 24.9 years and the highest percentage occurred between 23 and 26 years of age, followed by 27 years and more. Age at menarche ranged between 11 to 22 years for the majority women (average, 15.0). Almost 50% of the women experienced menopause at the age of 50 years (average, 48.5).

Marital status was significantly associated with OC mortality in both age-adjusted and multivariable-adjusted models (Table 2). For instance, single marital women revealed a significantly higher RR of OC mortality in age-adjusted (RR, 4.11; 95% CI, 1.66 to 10.23; p=0.002) and multivariable-adjusted (RR,

Table 1. Information of adjusted variables

Category	No.	Frequency		PYs and death rate/100,000 PYs	
		OC death	p-value	PYs	Death rate
Age of women (yr)			0.778		
40–44	7,535	13		137,876	9.43
45–49	7,912	8		142,312	5.62
50–54	9,087	15		163,145	9.19
55–59	10,791	16		186,994	8.56
60–64	11,101	22		179,668	12.24
65–69	8,589	10		129,484	7.72
70–74	5,547	9		73,725	12.21
75–79	3,623	5		40,342	12.39
Age at highest education (yr)			0.486		
6–15	19,074	26		297,818	8.73
16–18	23,804	37		386,806	9.57
19+	4,718	4		77,464	5.16
Family history of cancer*			0.683		
No	63,206	97		1,037,715	9.35
Yes	979	1		15,831	6.32
Past history of hypertension			0.766		
No	43,768	63		744,441	8.46
Yes	13,540	18		206,119	8.73
Past history of diabetes			0.800		
No	53,162	77		893,106	8.62
Yes	2,404	3		32,064	9.36
Past history of operation			0.846		
No	31,142	47		50,819	9.25
Yes	22,853	33		362,727	91.00
Sports (hr/wk)			0.097		
5–6	2,357	3		37,291	8.04
3–4	2,774	1		44,673	2.24
1–2	7,041	5		114,718	4.36
<1	38,837	65		635,578	10.23
Walking (min/day)			0.631		
>60	24,816	34		411,367	8.27
30–60	10,016	16		159,103	10.06
<30	8,580	17		132,922	12.79
A little	5,237	7		83,597	8.37
Smoking			0.841		
Current smoker	3,066	4		47,792	8.37
Ex-smoker	963	2		13,970	14.32
Non-smoker	51,452	71		857,337	8.28
Drinking alcohol			0.642		
Current drinker	14,189	17		237,071	7.17
Ex-drinker	992	2		14,489	13.80
Non-drinker	42,913	64		704,966	9.08

Total sample varied due to missing information.
OC, ovarian cancer; PYs, person-years.
*Breast, endometrial, and ovarian cancer for mother and sister and prostate cancer for father and brother.

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Table 2. Adjusted relative risk for ovarian cancer mortality in relation to reproductive and other factors in Japan

Variable	Category	Frequency		PYs and death rate/100,000 PYs		Model I: age adjusted RR for OC death including 95% CI and p-value			Model II: multivariable adjusted RR for OC death including 95% CI and p-value		
		Subjects	OC death	PYs	Death rate	RR	95% CI	p-value	RR	95% CI	p-value
Marital status	Married	45,344	65	766,555	8.48	1.00			1.00		
	Widow/divorcee	8,788	11	128,596	8.55	0.95	0.49–1.86	0.883	0.65	0.19–2.21	0.493
	Single	885	5	14,288	34.99	4.11	1.66–10.23	0.002	5.54	1.68–18.22	0.005
Age at marriage excluding single marital women[2]	11–19	3,528	5	53,867	9.28	1.12	0.45–2.82	0.811	1.64	0.49–5.53	0.422
	20–25	38,325	51	635,389	8.03	1.00			1.00		
	26+	10,279	19	174,924	10.86	1.35	0.79–2.28	0.271	1.09	0.49–2.42	0.834
	p-trend							0.405			0.789
No. of pregnancy excluding single marital women	0	1,415	3	22,352	13.42	1.00			1.00		
	1–2	14,328	21	244,553	8.59	0.64	0.19–2.18	0.479	0.64	0.14–2.90	0.561
	3–4	23,937	36	402,389	8.95	0.66	0.20–2.15	0.491	0.45	0.10–1.99	0.293
	5+	10,581	8	165,327	4.84	0.36	0.09–1.35	0.128	0.58	0.12–2.83	0.504
	p-trend							0.149			0.487
No. of live birth excluding single marital women	0	1,455	3	22,689	13.22	1.00			1.00		
	1–2	22,980	33	388,636	8.49	0.65	0.20–2.15	0.484	0.60	0.14–2.61	0.491
	3–4	21,136	30	354,063	8.47	0.63	0.19–2.07	0.448	0.56	0.13–2.49	0.450
	5+	4,034	2	57,357	3.49	0.25	0.04–1.57	0.139	0.28	0.02–3.34	0.317
	p-trend							0.267			0.429
Age at first delivery excluding non-parous women	11–22	11,084	20	173,183	11.55	1.00			1.00		
	23–26	27,205	34	452,013	7.52	0.68	0.39–1.18	0.164	0.36	0.16–0.80	0.012
	27+	12,897	20	216,247	9.25	0.83	0.45–1.54	0.837	0.59	0.25–1.38	0.221
	p-trend							0.581			0.242
Age at menarche	6–14	24,665	31	414,134	7.49	1.00			1.00		
	15–16	22,189	35	365,759	9.57	1.26	0.76–2.10	0.371	1.22	0.60–2.48	0.588
	17+	11,081	18	178,159	10.10	1.29	0.69–2.42	0.426	1.16	0.45–2.99	0.766
	p-trend							0.382			0.687
Age at menopause	<50	19,562	29	312,864	9.27	1.00			1.00		
	50+	21,860	32	348,005	9.20	0.92	0.55–1.53	0.748	0.90	0.41–1.97	0.800
History of hormonal drug use	Yes	2,428	4	38,856	10.29	1.00			1.00		
	No	45,819	67	751,601	8.91	0.86	0.31–2.36	0.766	0.95	0.23–3.98	0.948
Body mass index	Underweight	3,827	7	56,641	12.36	1.48	0.67–3.26	0.331	1.00	0.23–4.22	0.995
	Normal	42,519	57	707,154	8.06	1.00			1.00		
	Overweight	13,652	24	227,413	10.55	1.31	0.81–2.12	0.266	1.53	0.76–3.09	0.232
	p-trend							0.662			0.279

OC, ovarian cancer; PYs, person-years; RR, relative risk.

Table 3. Results of age-adjusted Cox models for two mutually exclusive groups of women based on the cut-off of age 50 at baseline

Variable	Below 50 yr of age			Age 50 yr and above		
	Age adjusted RR	95% CI	p-value	Age adjusted RR	95% CI	p-value
Marital status						
Married	1.00			1.00		
Widow/divorcee	1.11	0.15–8.37	0.917	0.95	0.12–6.13	0.880
Single	3.07	0.41–23.08	0.275	4.58	1.65–12.72	0.003
Body mass index						
Normal	1.00			1.00		
Underweight	1.22	0.16–9.33	0.848	1.53	0.65–3.61	0.334
Overweight	2.1	0.84–5.27	0.115	1.12	0.64–1.96	0.687
p-trend	0.177			0.834		
No. of pregnancy						
0	1.00			1.00		
1–2	0.37	0.05–2.98	0.351	0.74	0.17–3.30	0.691
3–4	0.34	0.04–2.68	0.306	0.82	0.19–3.45	0.783
5+	-	-		0.51	0.11–2.42	0.401
p-trend	0.137			0.414		
No. of live birth						
0	1.00			1.00		
1–2	0.39	0.05–3.03	0.37	0.75	0.17–3.22	0.696
3–4	0.27	0.03–2.30	0.23	0.82	0.19–3.47	0.789
5+	-	-	-	0.32	0.04–2.31	0.258
p-trend	0.265			0.510		
Age at first delivery						
11–22	1.00			1.00		
23–26	0.78	0.21–2.94	0.714	0.66	0.36–1.22	0.185
27+	1.41	0.35–5.64	0.627	0.70	0.35–1.43	0.327
p-trend	0.500			0.323		

Not estimated due to insufficient number of ovarian cancer death.
CI, confidence interval; RR, relative risk.

5.54; 95% CI, 1.68 to 18.22; p=0.005) models as compared to married women. Although overweight women revealed an elevated risk of OC mortality as compared to normal BMI in both models, they were statistically insignificant.

The age-adjusted Cox-model revealed reduced but insignificant association of OC mortality with higher number of pregnancy and higher number of live birth as compared to the null category. For example, the age-adjusted RR for the category of 1–2, 3–4, and 5+ pregnancies were 0.64 (95% CI, 0.19 to 2.18), 0.66 (95% CI, 0.20 to 2.15), and 0.36 (95% CI, 0.09 to 1.34) when compared with the category of nullipregnancy (Table 2). Later age at menarche was also found to be associated with an elevated risk of OC mortality (Table 2).

Group-specific analyses based on the baseline age (Table 3) showed a strong and significant association between single marital status and OC mortality among the women of 50+ years of age at baseline (RR, 4.58; 95% CI, 1.65 to 12.72; p=0.003). In contrast, the association was insignificant among the younger women aged less than 50 years (RR, 3.07; 95% CI, 0.41 to 23.08; p=0.275).

DISCUSSION

According to our results, only marital status was strongly associated with OC mortality, with a four-time higher risk among women with single marital status. The effect of single marital status was stronger among older (aged 50+ years at

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baseline) than younger women. Nulliparous and nullipregnant women also experienced elevated risks of OC mortality. Lower risks of OC mortality due to higher pregnancies or a higher risk due to nulliparity were reported in other studies [13,19,21]. A lower number of birth/pregnancy is obviously associated with a prolonged birth spacing or time to pregnancy, which may act as risk factors. For instance, a higher risk of OC was found among those women who gave last birth before 10 years as compared to women who gave last birth within five years of diagnosis [16]. Similarly, an increased ovarian cancer risk with a prolonged time to pregnancy was found by Braem et al. [13]. The average age at marriage at baseline (23.4 years) seems to be low according to the present situation. However, it is not surprising because the data reflected the situation of the period of 1988 to 1991.

Although additional research is recommended to elucidate the different biologic pathways of OC [13], according to present knowledge, reproductive factors such as pregnancies or some components of the child bearing process can protect OC by several mechanisms [13,21]. The two commonly suggested etiologic mechanisms for OC are (1) that suppression of ovulation reduces risk and (2) that suppression of pituitary gonadotropins reduces risk. Parity might reduce OC risk by increasing the circulation of progesterone levels [13]. A pregnancy may lead to anovulation, thereby can reduce gonadotropin secretion and increase endogenous estrogen and progesterone levels. An increasing progesterone level can protect the OC development by suppressing the epithelial proliferation, promoting cellular differentiation and apoptosis. Moreover, pregnancies and apoptosis resulting from the high progesterone levels during pregnancy or from exogenous hormone can clear malignantly transformed cells from the ovaries [13,21].

Other reproductive factors provided mixed results. For instance, our study failed to show any significant association between age at delivery and OC mortality, although some studies reported that higher age at first birth is positively associated with OC [16,19]. Similarly, several epidemiological studies which examined the impact of age at menarche and age at menopause on epithelial OC provided inconclusive results [13,16]. Although some studies provided the evidence of higher risk in relation to age at menarche and menopause [19,37], the JACC study failed to provide such evidence. Results are also inconsistent for hormonal drug use as our study revealed no association with OC, whereas others reported higher risks [19,21]. It is explained that an excessive stimulation of ovarian tissue by hormones may increase the OC risk [13].

Being underweight and overweight also showed age-adjusted elevated risks for OC mortality. Results connecting the obesity and OC are also mixed. Many studies suggested that excess body weight is a risk factor for many cancers [18,22,38,39]. The association was heterogeneous and stronger in case-control studies than in prospective studies [18]. For instance, height (≥170 cm) and BMI were found to be associated with an increased risk of OC in premenopausal women [18]. Overweight women showed significantly increased risk of OC mortality in Denmark [40]. Several interacting metabolic and hormonal pathways of insulin-resistance could be responsible for the underlying association between excess body weight and cancer [38]. However, no association was also reported by other studies [39].

Briefly, other investigated factors such as education [16], smoking [5,14,19,22,23], alcohol drinking [14,22,24-26], physical activity (sports, walking) [14,22,27-29], and family history of cancer [15,16,21,40] are still inconsistent.

Despite of many strengths mentioned in the introduction, this study has also several limitations. Some of the important factors mentioned by others are not studied, because of data unavailability. For instance, we did not study the association of oral contraceptives and OC mortality, although this factor found as a protective factor by other studies [13,16,37]. Hysterectomy, tubal ligation [13], higher number of abortions [16] and breastfeeding [21] were also found to be protective. Our analyses are based on baseline data and hence we did not consider any changes in investigated factors (e.g., smoking, and drinking). This also may limit our findings as subjects can change their behaviors any time during the long follow-up period. Finally, missing information for different variables which vary from 6.5% (BMI) to 35.5% (age at menopause) may affect the power of the study.

Our significant findings may indicate several implications. For instance, the rate of women remaining single is increasing in Japan, which may cause an increased burden for OC in the future. Similarly, decreasing number of pregnancies and births per woman can also contribute to the higher burden of OC in Japan [10,17]. Likewise, population ageing can contribute to the increasing burden of OC in Japan.

In conclusion, our study revealed both consistent and inconclusive results. Only women with single marital status experienced a significantly higher risk of OC mortality. Although many studies reported higher risks for nulliparous and nullipregnant women, these results are still inclusive in Japan. Other factors also provided inconsistent results when compared with other studies. Despite of these inconsistencies, our findings could still be taken as an important reference because of its strengths in terms of large and representative sample, reliability, and long follow-up.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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