The presence of chronic diseases contributes to the occurrence risk factors for gynecological cancers in Japan

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Received May 14, 2019; Accepted January 2, 2020

DOI: 10.3892/mco.2020.1989

Abstract. The aim of the present study was to determine whether chronic diseases (CD), such as hypertension, diabetes mellitus, dyslipidemia, heart diseases and cerebrovascular diseases, are occurrence risk factors and affect the survival of patients with gynecological cancers (GC). The correlations between CD and the characteristics and survival of 1,590 GC patients [685 with cervical cancer (CC), 613 with endometrial cancer (EM) and 292 with ovarian cancer (OV)] were investigated in the present study. Of the CD patients, 189 had CC (27.6%), 265 had EM (43.2%) and 72 had OV (24.7%). The incidence of CD increased with age in GC patients. The number of CD patients aged ≥70 years, was 8.6-fold higher in the CC group, 3.0-fold higher in the EM group, and 9.6-fold higher in the OV group compared with those aged <50 years. CD and excess body weight were associated with GC regardless of patient age. However, there was no correlation between CD and survival at any age in GC patients. These findings indicate that CD contribute to >24% of the occurrence risk factors in GC patients in Japan.

Introduction

The incidence of gynecological cancers (GC) has increased in Japan, with an estimated 30,964 newly diagnosed patients in 2009. In recent years, the incidence of GC has increased among younger patients, as well as among older patients (1). The risk factors for GC differ by organ. For example, the development of invasive cervical cancer (CC) requires persistent infection by human papillomavirus (2,3). Several occurrence risk factors for endometrial cancer (EM) have been established, including excess body weight (4) and diabetes mellitus (DM) (5). The occurrence risk factors for ovarian cancer (OV) include age at diagnosis, family history of OV, infertility treatment and assisted fertilization, obesity and metabolic syndromes (6). Recently, metabolic conditions, such as obesity, hyperlipidemia and DM, have been attracting increasing attention with respect to OV incidence (7,8). Therefore, the onset of EM and OV appears to be associated with lifestyle and behavioral factors, such as dietary habits, physical activity, smoking and alcohol consumption.

Chronic diseases (CD) and cancer share common risk factors, including aging and unhealthy habits, such as smoking, poor diet, sedentary lifestyle, obesity and alcohol intake. CD include hypertension (HT), DM, dyslipidemia (DL), heart disease (HD) and cerebrovascular disease (CVD), and constitute >20% of the occurrence risk factors for various cancers (9). In 2017, the Japanese Ministry of Health, Labour and Welfare reported that 108,000 CD patients were aged <35 years, 3,141,000 CD patients were aged 35-64 years, and 11,458,000 CD patients were aged ≥65 years among women without cancer in Japan (10).

The development rates of CD are rapidly increased by excess body weight (11), but there are no published details of the effect of CD on GC. Therefore, the aim of the present study was to investigate the correlations between CD and GC, including CC.

Patients and methods

Study population. The present retrospective study reviewed the medical records of 1,590 GC patients who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital (Okayama, Japan) between April 2004 and December 2017. The study protocol was approved by the Institutional Review Board of Okayama University Hospital (1904-05). Several studies reported that the threshold for lowest risk of all-cause mortality was ~100 g alcohol/week and <10 cigarettes/day (12,13). All patients underwent a review of their medical history and lifestyle habits (smoking-positive: Current smokers of ≥10 cigarettes/day; alcohol intake-positive: Alcohol intake of ≥14 g/day), physical examination and routine clinical staging. The patients were treated according to the Japan Society of Gynecologic Oncology clinical

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Key words: gynecological cancer, chronic diseases, occurrence risk factors

Table I. Incidence of GC among patients with chronic diseases in different age groups.

	CC		EM		OV	
Chronic diseases	Number	(%)	Number	(%)	Number	(%)
HT, age (years)						
<50	9	3.2	12	10	1	1.3
50-59	16	11.6	34	17	13	14.9
60-69	43	32.3	61	48.8	19	23.2
≥70	57	41.6	67	39.9	13	28.9
DM, age (years)						
<50	4	1.4	13	10.8	2	2.6
50-59	10	7.2	17	8.5	3	3.4
60-69	15	11.2	20	16	4	4.9
≥70	12	8.8	31	18.5	6	13.3
DL, age (years)						
<50	2	0.7	5	4.2	0	0
50-59	4	2.9	18	9	8	9.2
60-69	14	10.5	27	21.6	8	9.8
≥70	14	10.2	42	25	7	15.6
HD, age (years)						
<50	2	0.7	4	3.3	1	1.3
50-59	2	1.4	6	3	2	2.3
60-69	4	3	13	10.4	1	1.2
≥70	15	10.9	8	4.8	2	4.4
CVD, age (years)						
<50	3	1.1	0	0	0	0
50-59	2	1.4	5	2.5	0	0
60-69	6	4.5	6	4.8	3	3.7
≥70	13	9.5	6	3.6	3	6.7

GC, gynecological cancers; CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; HD, heart diseases; CVD, cerebrovascular diseases.

guidelines (14-16). The treatment options for gynecological cancer included surgery, radiotherapy and/or chemotherapy, depending on tumor stage and additional risk factors.

Data collection. The patients were asked to complete questionnaires on their history of cardiac disease, lifestyle habits (smoking and alcohol intake), and medications for HT, DM and DL. The measurements included standard medical examinations, such as height, weight, blood pressure, fasting blood glucose, hemoglobin A1c and serum lipid profile, including triglyceride (TG), serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels. Patients with HT were defined as those with blood pressure ≥140/90 mmHg, or those on antihypertensive medication. Patients with DM were defined as those with hemoglobin A1c ≥6.5%, or those receiving antidiabetic medication. Patients with DL were determined as those with TG ≥150 mg/dl, HDL-C <40 mg/dl, and LDL-C ≥140 mg/dl, or those receiving medication for DL. The presence of HD and CVD were assessed based on self-reports. Height and weight were measured on admission, prior to any therapeutic intervention. Body mass index (BMI) was defined according to the 2015 World Health Organization classification as follows: Underweight, <18.5 kg/m^2; normal weight, 18.5-24.99 kg/m^2; overweight, 25.0-29.99 kg/m^2; and obese, ≥30.0 kg/m^2.

Statistical analysis. Data were analyzed using χ^2 and Mann-Whitney U-tests for comparisons, and by one-way analysis of variance followed by Fisher's protected least significant difference test for all pairwise comparisons. Survival curves were constructed using the Kaplan-Meier method, and differences between survival curves were examined using the log-rank test. Analyses were performed using SPSS software, version 23.0 (IBM Corp.), with the significance level set at 0.05.

Results

Patient characteristics. CC, EM and OV patients were aged 25-92, 23-91 and 15-84 years, respectively (median CC age, 55.0 years; median EM age, 59.0 years; and median OC age, 57.0 years). Age was divided into four groups: <50, 50-59,

Table II. Baseline characteristics and CD in patients with gynecological cancers.

Baseline characteristics	CC			EM			OV		
	Number	(%)	P-value	Number	(%)	P-value	Number	(%)	P-value
Stage			-			<0.001[a]			<0.001[a]
I, II	437	63.8		460	75.0		139	47.6	
III, IV	248	36.2		153	25.0		153	52.4	
HT			-			<0.001[a]			0.375
Present	125	18.2		174	28.4		46	15.8	
Absent	560	81.8		439	71.6		246	84.2	
DM			-			<0.001[a]			0.601
Present	41	6		81	13.2		15	5.1	
Absent	644	94		532	86.8		277	94.9	
DL			-			<0.001[a]			0.075
Present	34	5		92	15.0		23	7.9	
Absent	651	95		521	85.0		269	92.1	
HD			-			0.126			0.272
Present	23	3.4		31	5.1		6	2.1	
Absent	662	96.6		582	94.9		286	97.9	
CVD			-			0.453			0.229
Present	24	3.5		17	2.8		6	2.1	
Absent	661	96.5		596	97.2		286	97.9	
BMI, kg/m^2			-			<0.001[a]			0.537
<25.0	549	80.1		370	60.4		239	81.8	
≥25.0	136	19.9		243	39.6		53	18.2	
Smoking			-			<0.001[a]			<0.001[a]
Negative	524	76.5		577	94.1		274	93.8	
Positive	161	23.5		36	5.9		18	6.2	
Alcohol			-			<0.001[a]			0.026[a]
Negative	609	88.9		580	94.6		273	93.5	
Positive	76	11.1		33	5.4		19	6.5	

[a]Statistically significant difference. CD, chronic diseases; CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer; BMI, body mass index, HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; HD, heart diseases; CVD, cerebrovascular diseases.

60-69 and ≥70 years. The <50 years group included 277 CC (40.4%), 120 EM (19.6%) and 78 OV (26.7%) patients; the 50-59 years group included 138 CC (20.2%), 200 EM (32.6%) and 87 OV (29.8%) patients; the 60-69 years group included 133 CC (19.4%), 168 EM (27.4%) and 82 OV (28.1%) patients; and the ≥70 years group included 137 CC (20.0%), 125 EM (20.4%) and 45 OV (15.4%) patients.

The HT, DM, DL, HD and CVD patients in the <50 years group included 9, 4, 2, 2 and 3 CC patients, respectively (3.2, 1.4, 0.7, 0.7 and 1.1%, respectively); 12, 13, 5, 4 and 0 EM patients, respectively (10.0, 10.8, 4.2, 3.3 and 0%, respectively); and 1, 2, 0, 1 and 0 OV patients, respectively (1.3, 2.6, 0, 1.3 and 0%, respectively). The HT, DM, DL, HD and CVD patients in the 50-59 years group included 16, 10, 4, 2 and 2 CC patients, respectively (11.6, 7.2, 2.9, 1.4 and 1.4%, respectively); 34, 17, 18, 6 and 5 EM patients, respectively (17.0, 8.5, 9.0, 3.0 and 2.5%, respectively); and 13, 3, 8, 2 and 0 OV patients, respectively (14.9, 3.4, 9.2, 2.3 and 0%, respectively).

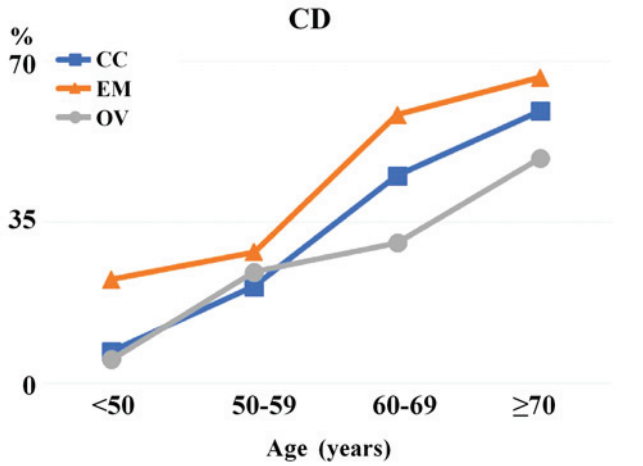

Figure 1. The percentage of chronic diseases (CD) in cervical cancer (CC), endometrial cancer (EM) and ovarian cancer (OV) patients was examined in the four age groups: <50, 50-59, 60-69 and ≥70 years.

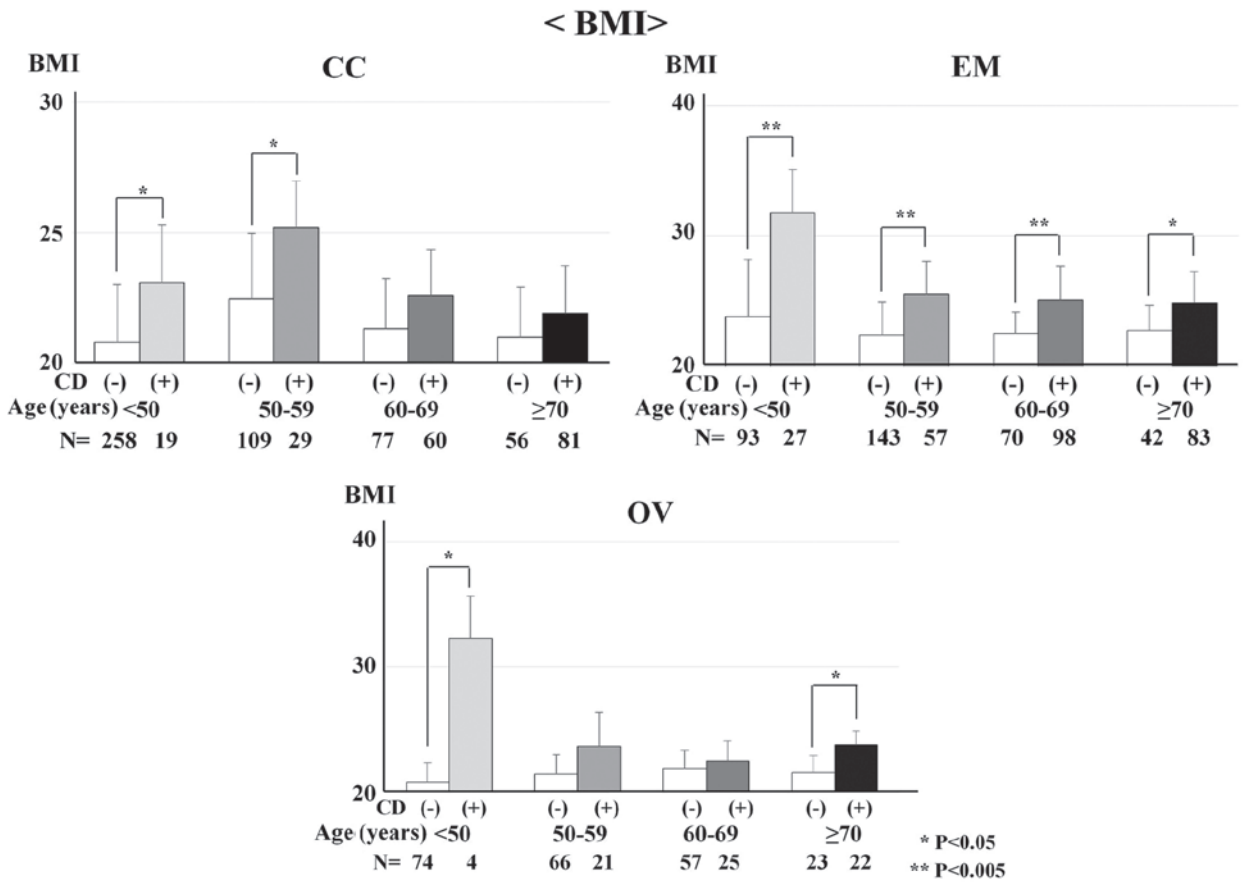

Figure 2. The association of body mass index (BMI) with chronic diseases (CD) and age (four groups: <50, 50-59, 60-69 and ≥70 years) was examined in cervical cancer (CC), endometrial cancer (EM) and ovarian cancer (OV) patients. *P<0.05; **P<0.005.

The HT, DM, DL, HD and CVD patients in the 60-69 years group included 43, 15, 14, 4 and 6 CC patients, respectively (32.3, 11.2, 10.5, 3.0 and 4.5%, respectively); 61, 20, 27, 13 and 6 EM patients, respectively (48.8, 16.0, 21.6, 10.4 and 4.8%, respectively); and 19, 4, 8, 1 and 3 OV patients, respectively (23.2, 4.9, 9.8, 1.2 and 3.7%, respectively). Finally, the HT, DM, DL, HD and CVD patients in the ≥70 years group included 57, 12, 14, 15 and 13 CC patients, respectively (41.6, 8.8, 10.2, 10.9 and 9.5%, respectively); 67, 31, 42, 8 and 6 EM patients, respectively (39.9, 18.5, 25.0, 4.8 and 3.6%, respectively); and 13, 6, 7, 2 and 3 OV patients, respectively (28.9, 13.3, 15.6, 4.4 and 6.7%, respectively) (Table I).

The associations of each GC type [CC (n=685), EM (n=613) and OV (n=292)] with clinical characteristics (cancer stage, HT, DM, DL, HD, CVD, BMI, smoking and alcohol intake) were assessed (Table II). Regarding FIGO stage, there were significantly more EM patients with early-stage disease compared with CC patients (P<0.001). Conversely, the number of advanced-stage OV patients was significantly higher compared with CC patients (P<0.001). The incidence of HT, DM, DL and high BMI were significantly higher in EM patients compared with CC patients (all P<0.001). Furthermore, significantly more CC patients were smoking- and alcohol intake-positive compared with EM and OV patients (P<0.001, P<0.001, P<0.001 and P=0.026, respectively).

The effect of CD was examined by determining how many of CC, EM and OV patients in each of the four age groups had CD. CD patients were divided into 189 CC (27.6%), 265 EM (43.2%) and 72 OV (24.7%) patients. Patients in the <50 years group with CD included 19 CC (6.9%), 27 EM (22.5%) and 4 OV (5.1%) patients. CD patients in the 50-59 years group included 29 CC (21.0%), 57 EM (28.5%) and 21 OV (24.1%) patients. CD patients in the 60-69 years group included 60 CC (45.1%), 98 EM (58.3%), and 25 OV (30.5%) patients. Finally, CD patients in the ≥70 years group included 81 CC (59.1%), 83 EM (66.4%) and 22 OV (48.9%) patients. CC patients aged ≥70 years and EM patients aged 60-69 and ≥70 years accounted for >50% of those with CD. Therefore, the number of patients with CD aged ≥70 years was 8.6-fold higher in the CC group, 3.0-fold higher in the EM group, and 9.6-fold higher in the OV group compared with patients aged <50 years (Fig. 1).

CD was examined for its association with BMI, smoking and alcohol intake at any age in CC, EM and OV patients. BMI and CD were significantly associated in CC patients aged <50 and 50-59 years (P=0.025 and P=0.010, respectively). BMI and CD were significantly associated in all age groups in EM patients (P<0.001, P<0.001, P<0.001 and P=0.014, respectively). BMI and CD were significantly associated in OV patients aged 50-59 and ≥70 years (P=0.043 and P=0.004, respectively; Fig. 2). However, there was no association between CD and smoking or alcohol intake at any age in CC, EM or OV patients.

In the present study, the median overall survival (OS) rates for patients with CC, EM and OV were 44.0, 40.0 and 32.5 months, respectively. The follow-up period was 1-174,

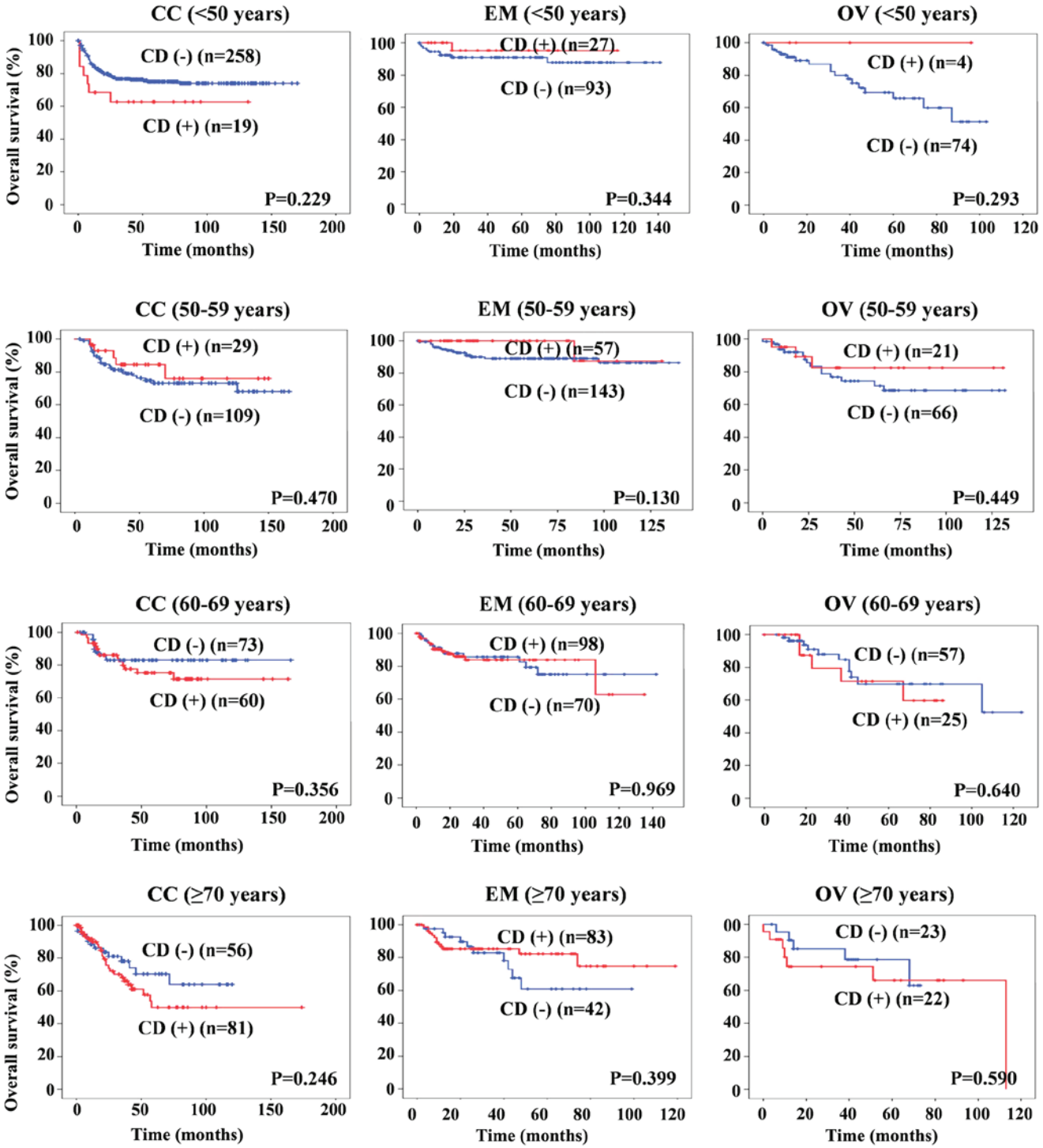

Figure 3. Kaplan-Meier curves for overall survival (OS) in relation to CD according to age (four groups: <50, 50-59, 60-69 and ≥70 years) in cervical cancer (CC), endometrial cancer (EM) and ovarian cancer (OV) patients.

1-146 and 1-132 months, respectively. The OS curves for the 1,590 GC patients according to their CD are shown in Fig. 3. There was no significant correlation between CD and survival at any age in CC, EM or OV patients.

Discussion

The occurrence risk factors for cancer include smoking, an unhealthy diet, obesity, sedentary lifestyle, DM, HT and alcohol abuse, either alone or in combination. Accumulating evidence has suggested that obesity is an important occurrence risk factor for EM, and BMI is significantly associated with symptoms in EM patients (17). Zhang *et al* also demonstrated that DM is associated with EM (5), and several studies have reported the association of metabolic markers of obesity, including elevated blood glucose, TG and total cholesterol levels, with EM (18).

CD and cancer share common risk factors, particularly those associated with an unhealthy lifestyle, such as smoking, an unhealthy diet, physical inactivity, obesity and alcohol

intake. CD is known to contribute to >20% of occurrence risk factors for various cancers (9); however, to the best of our knowledge, this is the first study to describe an association between CD and GC, including CC.

In the present study, CD, including HT, DM, DL, HD and CVD, were examined in patients with CC, EM and OV. For all diseases, we observed a high frequency of EM, CC and OV, in decreasing order. For example, HT was observed in 18.2, 28.4 and 15.8% of CC, EM and OV patients, respectively; DL was observed in 5.0, 15.0 and 7.9% of CC, EM and OV patients, respectively; DM occurred in 6.0, 13.2 and 5.1% of CC, EM and OV patients, respectively; HD was diagnosed in 3.4, 5.1 and 2.1% of CC, EM and OV patients, respectively; and CVD was recorded in 3.5, 2.8 and 2.1% of CC, EM and OV patients, respectively. Among the CD patients, 27.6, 43.2 and 24.7% had CC, EM and OV, respectively. The incidence of CD was found to increase with age in GC patients, with CC patients aged >70 years and EM patients aged >60 years accounting for >50% of patients with CD. Moreover, the numbers of any disease increased with increasing age, regardless of the number of CD.

CD were examined for their association with lifestyle factors, such as obesity, smoking and alcohol intake, at any age in all GC patients. In the present study, CD were more prevalent among EM patients compared with CC and OV patients. Among the CD patients, 27.6, 43.2 and 24.7% had CC, EM and OV, respectively. Of note, occurrence risk factors for EM have been established, including HT, DM and DL.

However, there was no association of smoking and alcohol intake with CD. We also determined whether CD were associated with outcome in GC patients, and found that the presence of CD was not a prognostic predictor for CC, EM or OV patients.

There were certain limitations to the present study. The number of patients was relatively small, and the examinations were performed at a single institution. Further prospective studies involving more patients and multiple institutions should provide more definitive data to verify the significance of our findings.

In conclusion, the presence of CD appears to contribute to >24% of the occurrence risk factors for GC patients in Japan.

Acknowledgements

The authors would like to thank all those who contributed to the present study, particularly the statisticians and colleagues of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. We appreciate their help with data management and statistical support. We would also like to thank Sarah Williams, PhD, and H. Nikki March, PhD for editing a draft of this manuscript.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

KN and KO contributed to the conception, design and conduction of the study, and analysis and interpretation of the data. HM, YM, JH, CO and HM contributed to data collection and the conduction of the study. All the authors have read and approved the final version of this manuscript.

Ethics approval and consent to participate

The present study was performed according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, and was approved by the Institutional Review Board of Okayama University Hospital (IRB approval no. 1904-005).

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests to disclose.

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