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Original Article

Risk of Gynecologic Cancer as Second versus First Primary Cancer in Japan

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This study aimed to determine whether the risk conferred by gynecologic cancer (GC) as second primary cancer (SPC) differs from that associated with GC as first primary cancer (FPC). We investigated the correlations between FPC/SPC and the characteristics and prognoses of 1,645 GC patients (701 with cervical cancer [CC], 641 with endometrial cancer [EM], and 303 with ovarian cancer [OV]). The χ^2 test and the Kaplan–Meier method were used to determine whether FPC/SPC and the characteristics and prognoses of GC patients. Of the SPC patients, 26 (3.7%) had CC, 53 (8.3%) had EM, and 31 (10.2%) had OV. The most common previous cancer type in SPC of GC patients was breast cancer, which was observed in 13 patients (50.0%) with CC, 23 (43.4%) with EM, and 16 (51.6%) with OV. In all patients with CC, EM, and OV as SPC, the stage was significantly associated with recurrence. There were no significant differences in the morbidity or mortality of CC, EM, or OV patients between those with FPC and those with SPC. The risk of SPC development in GC patients varied, ranging from 3.5% (CC) to 10.3% (OV) of patients.

Key words: second primary cancer, gynecologic cancer, prognosis

The incidence of gynecologic cancer (GC) has increased in Japan, with an estimated 30,964 patients newly diagnosed in 2009 [1]. Diagnostic techniques and treatment modalities have advanced, leading to earlier detection, improved disease management, and prolonged survival. Such improvements have caused a surge in the numbers of surviving patients with secondary primary cancer (SPC), posing an additional threat in terms of morbidity and mortality.

The criteria for diagnosing SPC are (i) each mass has definite malignant features; (ii) each mass can be separated from other masses; and (iii) the possibility of metastasis can be excluded [2]. The time interval of SPC occurrence is usually defined as synchronous if less than 6 months or metachronous if more than 6 months. Several studies have shown that the prognosis for metachronous SPC is better than that for synchronous SPC [3-5].

The Surveillance Epidemiology and End Results (SEER) program reported that SPC accounts for 7% of cervical cancer (CC) patients, 11% of endometrial cancer (EM) patients, and 5% of ovarian cancer (OV) patients [6]. However, SPC has not been identified as a prognostic factor in patients with GC. The present study therefore aimed to evaluate the correlations between SPC and both the clinical factors and prognosis of GC patients.

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Patients and Methods

This retrospective study reviewed the medical records of 1,645 GC patients (701 CC patients, 641 EM patients, and 303 OV patients) who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital between April 2004 and June 2018. The study protocol was approved by the Institutional Review Board of Okayama University Hospital (1906-021). Informed consent was obtained from all patients. The patients were treated in accordance with the clinical guidelines of the Japan Society of Gynecologic Oncology. Treatment options for gynecologic cancer included surgery, radiotherapy, and/or chemotherapy, depending on tumor stage and additional risk factors.

All patients underwent a review of their medical history, staging, histology, physical examination, family histology, and lifestyle (smoking and alcohol intake). Patient age was estimated based on the date of initial histologic diagnosis of cancer. Height and weight were measured upon hospital entry before any therapeutic treatment for gynecologic cancer. Body mass index (BMI) was defined according to the World Health Organization (WHO, 2015), and used to classify patients as underweight (< 18.4 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥ 30.0 kg/m^2). SPC was defined as two or more primary cancers occurring in an individual that were not an extension, recurrence, or metastasis.

Statistical analysis. Data were analyzed using the χ^2 and Mann–Whitney *U*-tests for multiple comparisons, and by one-factor analysis of variance followed by Fisher's protected least significant difference test for all pairwise comparisons. Morbidity and mortality curves were calculated by the Kaplan–Meier method, and differences between the curves were examined using the log-rank test. Analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) with a significance level of 0.05.

Results

Table 1 lists the baseline characteristics (age, stage, histology, BMI, and information regarding first-degree

Table 1 Patient and tumor characteristics

	CC		EM		OV	
	Numbers	(%)	Numbers	(%)	Numbers	(%)
Age (year)						
< 50	280	40	123	19.3	80	26.4
50–59	143	20.4	211	32.9	87	28.7
60–69	139	19.8	175	27.3	88	29
≥ 70	139	19.8	131	20.5	48	15.9
Stage						
I	291	41.5	435	67.9	128	42.3
II	159	22.7	51	8	13	4.3
III	186	26.5	95	14.8	106	35
IV	65	9.3	60	9.3	56	18.4
Histology						
CC; SCC, EM; Low type, OV; Serous Ca	526	75	419	65.4	120	4
CC; Non- SCC, EM; High type, OV; Non-serous Ca	175	25	222	34.6	183	96
BMI						
< 18.5	104	14.6	42	6.7	19	6.3
18.5–24.9	436	62.2	346	54	229	75.6
25.0–29.9	128	18.5	141	22	44	14.5
≥ 30.0	33	4.7	111	17.3	11	3.6
First-degree relative with cancer						
Negative	506	72.2	465	72.5	212	70
Positive	195	27.8	176	27.5	91	30
Smoking						
Negative	538	76.7	606	94.5	284	93.7
Positive	163	23.3	35	5.5	19	6.3
Alcohol						
Negative	619	88.3	607	94.7	284	93.7
Positive	82	11.7	34	5.3	19	6.3
Primary cancer						
First primary cancer	675	96.3	588	91.7	272	89.8
Second primary cancer	26	3.7	53	8.3	31	10.2

CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer; BMI, body mass index; SCC, squamous cell carcinoma; Ca, cancer.

relatives with cancer, smoking, and alcohol intake) of the CC, EM, and OV patients.

Among the GC patients, 1,535 (93.3%) had first primary cancer (FPC) and 110 (6.7%) had SPC. Of the SPC patients, 26 had CC (3.7%), 53 had EM (8.3%), and 31 had OV (10.2%). Correlations between each type of primary cancer (FPC or SPC) and clinical characteristics in GC (CC [n = 701], EM [n = 641], OV [n = 303]) patients were assessed. Patients with CC as SPC were significantly more likely to be elderly or nonsmokers than those with CC as FPC ($p < 0.001$ or $p = 0.004$, respectively). Family history (first-degree relative with cancer) was more frequently observed in patients with EM as SPC than those with EM as FPC ($p = 0.08$). However, there were no significant relationships between FPC and SPC for the other clinical characteristics assessed (Table 2).

Table 3 shows the distributions of the parameters examined according to the clinical characteristics of SPC in CC, EM, and OV patients. The most common previous cancer (history of first primary cancer) for SPC in GC patients was breast cancer. Breast cancer accounted for 13 patients (50.0%) with CC, 23 (43.4%) with EM, and 16 (51.6%) with OV. We investigated the time interval of other sites of FPC to SPC in GC patients. One patient with CC (3.8%), 15 with EM (28.3%), and 8 with OC (25.8%) were diagnosed with synchronous SPC. SPC in 11 patients with CC (42.3%), 30 patients with EM (54.7%), and 19 patients with OC (61.3%) were occurred within 5 years from PFC (Table 3).

Patients underwent follow-up examinations approximately every 1-2 months for the first 6 months, every 3 months for the next 2 years, and every 6 months thereafter. Median PFS and OS times for all patients in this study were 37.0 and 45.5 months with CC, 42.0 and 48.0 months with EM, and 23.0 and 38.0 months with OV, respectively; the range for follow-up periods was 1-166 months with CC, 1-166 months with EM, and 1-158 months with OV for both PFS and OS. At the last follow-up point, 491, 512, and 178 patients were alive with no evidence of disease; 138, 94, and 74 patients had died of disease; and 72, 35, and 51 patients were alive with disease for CC, EM and OV, respectively.

The correlations between clinical factors of SPC in CC, EM, or OV patients and progression-free survival (PFS) or overall survival (OS) were assessed in univariate and multivariate analyses (Table 4). In the univariate analysis of PFS and OS, stage was significantly associated with PFS ($p = 0.005$), whereas stage was significantly associated with OS ($p = 0.025$) in patients with CC as SPC. In the univariate analysis of PFS and OS, age ($p = 0.026$), time interval ($p = 0.026$), histology ($p = 0.017$), and stage ($p = 0.036$) were significantly associated with PFS, whereas age was significantly associated with OS ($p = 0.033$) in patients with EM as SPC. In the univariate analysis of PFS and OS, histology ($p = 0.001$) and stage ($p < 0.001$) were significantly associated with PFS ($p = 0.005$), whereas histology was significantly associated with OS ($p = 0.025$) in patients with OV as SPC. In the multivariate analysis, age was significantly associated with PFS in patients with EM as SPC. Furthermore, stage was significantly associated with PFS in patients with OV as SPC ($p = 0.002$).

Figure 1 shows the PFS and OS curves for the 1,645 GC patients according to their FPC and SPC statuses. There were no significant differences between FPC and SPC for recurrence or survival in CC, EM, or OV patients.

Discussion

GC is one of the most common cancers in females worldwide, but breakthroughs in diagnostic and therapeutic technologies have prolonged survival. According to some studies, as cancer survival rates have increased, the incidence of SPC has also gradually increased; this phenomenon appears to be due to a combination of genetic backgrounds and environmental effects [7-9]. This is the first study to attempt to determine whether SPC is related to poor prognosis in GC patients. In the present study, we investigated the frequency of SPC in patients with CC, EM, and OV. SPC was observed in 3.7% of CC patients, 8.3% of EM patients, and 10.2% of OV patients. Breast cancer was the most common previous cancer in patients with GC as SPC, accounting for approximately 50% of cases. We investigated the time interval from previous cancer to SPC in GC patients; 3.8% of CC patients, 28.3% of EM patients, and 25. 8% of OC patients were diagnosed with synchronous SPC. In this study, the recurrence and survival of patients exhibiting synchronous SPC were not significantly worse than those of patients with metachronous SPC.

It has been reported that the incidence of SPC increases with age [4, 10-12]. Increasing age is thought to increase the incidence of SPC due to the increased

Table 2 Tumor characteristics of second primary cancer compared with first primary cancer with gynecologic cancers

	CC			EM			OV		
	FPC n＝675	SPC n＝26		FPC n＝588	SPC n＝53		FPC n＝272	SPC n＝31	
	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value	Numbers	Numbers	*p*-value
Age (years)			＜0.001*			0.138			0.579
＜70	549	13		472	38		231	24	
≥70	126	13		116	15		41	7	
Stage			0.897			0.784			0.327
Early (Stage I–II)	433	17		445	41		124	17	
Advance (Stage III–IV)	242	9		143	12		148	14	
Histology			0.814			0.846			0.504
CC; SCC, EM; Low type, OV; Non-Serous Ca	507	19		385	34		106	14	
CC; Non- SCC, EM; High type, OV; Serous Ca	168	7		203	19		166	17	
BMI			0.248			0.409			0.375
＜30.0	642	26		484	46		263	29	
≥30.0	33	0		104	7		9	2	
First-degree relative with cancer			0.582			0.08			0.587
Negative	486	20		432	33		189	23	
Positive	189	6		156	20		83	8	
Smoking			0.004*			0.434			0.128
Negative	512	26		556	50		253	31	
Positive	163	0		32	3		19	0	
Alcohol			0.517			0.903			0.408
Negative	595	24		557	50		256	28	
Positive	80	2		31	3		16	3	

CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer; BMI, body mass index; FPC, first primary cancer; SPC, second primary cancer; SCC, squamous cell carcinoma; Ca, cancer.
*$p < 0.05$

Table 3 Tumor characteristics of second primary cancer with gynecologic cancers

	CC		EM		OV	
	Numbers	(%)	Numbers	(%)	Numbers	(%)
Second primary cancer						
Double	25	96.2	51	96.2	30	96.8
Triple	1	3.8	2	3.8	1	3.2
First primary cancer						
Breast cancer	13	50	23	43.4	16	51.6
Thyroid cancer	3	11.5	4	7.5	4	12.9
Colon cancer	5	19.2	6	11.3	4	12.9
Stomach cancer	2	7.7	4	7.5	1	3.2
Liver & Gallbladder cancer	0	0	3	5.7	0	0
Lung cancer	1	3.8	2	3.8	0	0
Cervical cancer	–	–	2	3.8	0	0
Ovarian cancer	0	0	6	11.3	–	–
Endometrial cancer	0	0	–	–	6	19.4
Hematologic marignanacy	0	0	2	3.8	0	0
Kidney cancer	1	3.8	2	3.8	1	3.2
Esophageal cancer	1	3.8	0	0	0	0
Other	1	3.8	1	1.9	0	0
Time Interval (years)						
＜−0.5 year	1	3.8	15	28.3	8	25.8
−1＜ to ≤−0.5 year	2	7.7	2	3.8	1	3.2
−3＜ to ≤−1 year	4	15.4	5	9.4	2	6.5
−5＜ to ≤−3 year	4	15.4	7	13.2	8	25.8
−10＜ to≤−5 year	5	19.2	9	17	4	12.9
≥−10 year	10	38.5	15	28.3	8	25.8

CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer.

Table 4 Prognostic factors for progression-free survival and overall survival of second primary cancer with gynecologic cancer selected by Cox's univariate and multivariate analysis

	CC			EM			OV		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
	Univariate analysis			Univariate analysis			Univariate analysis		
Progression free survival									
Age (over 70 years)	2.717	0.589–12.540	0.2	3.456	1.159–10.303	0.026*	1.082	0.292–4.007	0.906
FPC (breast cancer)	0.612	0.136–2.746	0.522	1.647	0.553–4.903	0.37	1.776	0.580–5.437	0.315
Time interval (< 5 years)	1.666	0.322–8.621	0.543	0.231	0.063–0.840	0.026*	0.481	0.155–1.489	0.204
First-degree relative with cancer	2.043	0.457–9.137	0.35	0.727	0.224–2.365	0.597	1.526	0.499–4.671	0.429
Histology (CC; Non-SCC, EM; High type, OV; Serous Ca)	0.022	0.000–12.789	0.239	4.221	1.297–13.732	0.017*	10.084	2.496–40.746	0.001*
Stage (Stage III-IV)	11.967	2.111–67.821	0.005*	3.224	1.082–9.605	0.036*	17.625	3.539–87.783	<0.001*
Overall Survival									
Age (over 70 years)	5.772	0.519–64.208	0.154	3.658	1.111–12.043	0.033*	1.817	0.332–9.947	0.491
FPC (breast cancer)	0.354	0.032–3.916	0.397	1.586	0.483–5.205	0.447	4.038	0.469–34.736	0.204
Time interval (<5 years)	1.079	0.098–11.937	0.95	0.429	0.125–1.467	0.177	0.709	0.142–3.544	0.675
First-degree relative with cancer	1.347	0.120–15.053	0.809	0.685	0.181–2.592	0.577	0.984	0.179–5.398	0.985
Histology (CC; Non-SCC, EM; High type, OV; Serous Ca)	0.021	0.000–271.476	0.422	2.296	0.700–7.535	0.17	12.209	1.371–108.75	0.025*
Stage (Stage III-IV)	15.916	1.413–179.257	0.025*	1.929	0.564–6.595	0.295	209.461	0.114–384415.206	0.163
	Multivariate analysis			Multivariate analysis			Multivariate analysis		
Progression free survival									
Age (over 70 years)		–		4.121	1.199–14.163	0.025*		–	
Time interval (< 5 years)		–		0.441	0.105–1.855	0.264		–	
Histology (CC; Non-SCC, EM; High type, OV; Serous Ca)		–		1.754	0.449–6.852	0.419	0.228	0.024–2.197	0.201
Stage (Stage III-IV)		–		3.428	0.941–12.480	0.062	74.593	4.927–1129.306	0.002*

CC, cervical cancer; EM, endometrial cancer; OV, ovarian cancer; FPC, first primary cancer; SCC, squamous cell carcinoma; Ca, cancer.
* $p < 0.05$.

cumulative exposure to various environmental factors and to the increased risk of genetic mutations. Furthermore, Yoshimoto *et al*. reported that family history is a factor that increases the incidence of SPC [13]. In this study, we investigated age and family history in patients with CC, EM, and OV as SPC. Patients with CC as SPC were significantly more likely to be elderly. And, family history tended to be more prevalent in patients with EM as SPC. This study investigated PFS and OS in patients with CC, EM, and OV as SPC. In all patients with GC (CC, EM, and OV) as SPC, stage was significantly associated with PFS. Only in patients with CC as SPC was stage significantly associated with OS. Moreover, multivariate analysis of our study population showed that stage was independently correlated with shorter PFS in patients with OV as SPC. Therefore, stage may be useful in projecting prognostic factors for patients with GC as SPC.

SPC is an important prognostic factor in breast cancer [14]. In this study, we also compared the prognoses of FPC and SPC in GC patients. There were no significant differences in the morbidity or mortality of CC, EM, or OV patients between those with FPC and those with SPC. We suggest that SPC was not a significant prognostic factor in GC patients.

We acknowledge that our study has some limitations. The number of patients was relatively small, and the examination was performed at a single facility. Further prospective studies with more patients are needed to provide more definitive data to help clarify the appropriate treatment for patients with GC as SPC.

In conclusion, SPC accounted for 3.7% of CC, 8.3% of EM, and 10.2%

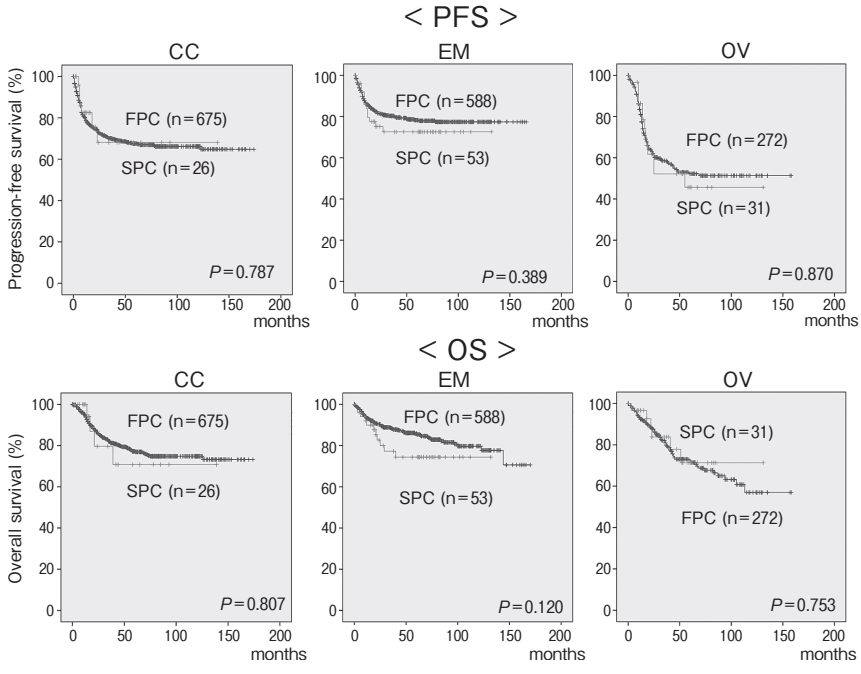

Fig. 1 Kaplan–Meier curves for progression-free survival (PFS) or overall survival (OS) according to first primary cancer (FPC) and second primary cancer (SPC) in CC, EM, and OV patients.

of OV in our subject group. There were no significant differences in the morbidity or mortality of CC, EM, or OV patients between those with FPC and those with SPC. Further, it is important to establish an appropriate treatment for patients with GC as SPC.

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