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# Secondary Primary Malignancy Risk in Patients With Ovarian Cancer in Taiwan

## *A Nationwide Population-Based Study*

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**Abstract:** To evaluate the incidence of secondary primary malignancy (SPM) in patients with ovarian cancer using a nationwide retrospective population-based dataset.

Patients newly diagnosed with ovarian cancer between 1997 and 2010 were identified using Taiwan's National Health Insurance database. Patients with antecedent malignancies were excluded. Standardized incidence ratios (SIRs) for SPM were calculated and compared with the cancer incidence in the general population. Risk factors for cancer development were analyzed using Cox proportional hazard models. Effects of surgery, chemotherapy, and radiotherapy after ovarian cancer diagnosis were regarded as time-dependent variables to prevent immortal time bias.

During the 14-year study period (follow-up of 56,214 person-years), 707 cancers developed in 12,127 patients with ovarian cancer. The SIR for all cancers was 2.78 (95% confidence interval 2.58–3.00). SIRs for follow-up periods of >5, 1–5, and <1 year were 1.87, 2.04, and 6.40, respectively. After the exclusion of SPM occurring within 1 year of ovarian cancer

diagnosis, SIRs were significantly higher for cancers of the colon, rectum, and anus (2.14); lung and mediastinum (1.58); breast (1.68); cervix (1.65); uterus (7.96); bladder (3.17), and thyroid (2.23); as well as for leukemia (3.98) and others (3.83). Multivariate analysis showed that age  $\geq$  50 years was a significant SPM risk factor (hazard ratio [HR] 1.60). Different treatments for ovarian cancer, including radiotherapy (HR 2.07) and chemotherapy (HR 1.27), had different impacts on SPM risk.

Patients with ovarian cancer are at increased risk of SPM development. Age  $\geq$  50 years, radiotherapy, and chemotherapy are independent risk factors. Close surveillance of patients at high risk should be considered for the early detection of SPM.

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**Abbreviations:** 5-FU = 5-fluorouracil, CI = confidence interval, HR = hazard ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Dataset, SIR = standardized incidence ratio, SPM = secondary primary malignancy.

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Using the largest nationwide population-based Asian dataset examined to date, this study revealed an increased cancer risk in patients with ovarian cancer, with a standardized incidence ratio (SIR) of 8.13 (95% confidence interval 6.52–10.02) among patients aged 20–39 years at the time of ovarian cancer diagnosis. SIRs for different cancer sites and risk factors were determined. The study is based in part on data from the National Health Insurance Research Database, provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes. The interpretations and conclusions reported herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes. Y-PH and C-JL contributed equally to this manuscript.

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## INTRODUCTION

Ovarian cancer is the seventh most common cancer in women worldwide, with about 239,000 new cases diagnosed in 2012.<sup>1</sup> The 5-year survival rate ranges approximately from 30% to 50%.<sup>1</sup> Advances in screening, surgery technique, and chemotherapy have improved survival in recent years. However, subsequent cancer risk is a concern because secondary primary malignancy (SPM) impacts patient survival.<sup>2–4</sup>

Several studies have reported SPMs in patients with ovarian cancer. A case-control study conducted in Germany determined that the risk of leukemia was increased 10-fold in patients with ovarian cancer who had undergone chemotherapy.<sup>5</sup> A Canadian cohort of patients with early ovarian cancer also showed a significant increase in SPM occurrence.<sup>6</sup> A population-based study that assessed 11,802 patients with ovarian cancer in the UK during 1961–1980 revealed a small increase in the rate of secondary malignancy.<sup>7</sup> A population-based study in Switzerland showed a marginally increased standardized incidence ratio (SIR) for SPM after exclusion of synchronous cases.<sup>8</sup> However, a Swedish group suggested that these increased risks reflect overestimation.<sup>9</sup> Due to the inconsistency of results and the lack of data from Asia, we conducted a retrospective population-based study examining SPM after the occurrence of ovarian cancer in Taiwan.

The National Health Insurance Research Dataset (NHIRD) in Taiwan provides nationwide population data to investigators for health research. As all patients with cancers are registered precisely, the NHIRD is suitable for the analysis of SPM. In addition to patients' age and sex, the NHIRD provides information about major surgeries, chemotherapy, radiotherapy, and comorbidities, which were not gathered and analyzed in most previous studies of ovarian cancer. The aim of this study was to

compare the overall incidence of SPM among patients with ovarian cancer with the expected incidence in the general population within the same age, sex, and calendar year using the NHIRD. In addition, we investigated the potential predisposition of patients with ovarian cancer to SPM with respect to chemotherapy, radiotherapy, and comorbidities.

## METHODS

### Data Sources

Taiwan's mandatory and universal National Health Insurance (NHI) program was initiated in 1995. The program covers more than 99% residents in Taiwan with comprehensive medical care.<sup>10</sup> It provides coverage for outpatient, emergency, inpatient, dental, and traditional Chinese medicine services, as well as prescription drugs.

Our study was based on data from the NHIRD, which is managed and made available publicly by the National Health Research Institute of Taiwan. We utilized the NHIRD's Registry of Catastrophic Illness, which provides comprehensive information on NHI enrollment and health care resource provision for all patients with severe diseases who receive copayment exemptions under the NHI program. It integrates several NHI databases, including claims data, NHI enrollment files, and the drug prescription registry. Ovarian cancer and all other types of malignancy are categorized as catastrophic illnesses. All information that would potentially enable the identification of individual patients is encrypted. These data are confidential, as mandated by the Bureau of NHI and the National Health Research Institute. Because the NHI dataset contains unidentifiable secondary data for research purposes, the institutional review board of Taipei Veterans General Hospital exempted this study from full review (2013-10-002CE).

### Study Population

For this nationwide population-based cohort study, patients with newly diagnosed ovarian cancer (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 183) in the period January 1, 1997 to December 31, 2010 were identified from the Registry of Catastrophic Illness. Patients diagnosed with ovarian cancer before January 1, 1997 were excluded. Patients who were younger than 20 years at the time of diagnosis and those who had antecedent malignancies were excluded. The main outcome we are willing to observe was development of SPM. For subjects identified by the Registry of Catastrophic Illness, the malignant diagnosis needs to be confirmed by histological evidence. Every patient was followed until the end of the study, occurrence of SPM, death, or dropout from the NHI program. The treatment modalities, such as surgery, radiation, and chemotherapy, and the medical comorbidities of these patients were collected for further analysis.

### Statistical Analyses

The SIR, defined as the observed number of target event occurrences divided by the expected ones, was used to determine the risk of SPM in our study cohort. The expected number of cancer occurrences was obtained by multiplying the cancer incidence in the general population (retrieved from Taiwan's National Cancer Registry) by patient number in the corresponding age group in the study cohort. Assuming that the cancer occurrence followed a Poisson probability distribution, 95% confidence intervals (CIs) of SIRs were estimated. The study cohort was stratified by age and the period of SPM development. Further subgroup analysis was performed. SIRs for

**TABLE 1.** Characteristics of Patients With Ovarian Cancer

	Total
No. of patients	12,127
Person-years at risk	56,214
Median follow-up, yr (interquartile range)	3.48 (1.54–7.00)
Median age, yr (interquartile range)	50 (42–61)
Treatment	
Surgery	8221 (67.8%)
Chemotherapy	8935 (73.7%)
Radiotherapy	1508 (12.4%)
Chemotherapy and radiotherapy	1414 (11.7%)
Age at diagnosis, yr	
20–39	2619 (21.6%)
40–59	6312 (52.0%)
60–79	2836 (23.4%)
≥80	360 (3.0%)
Chemotherapy agents	
Cyclophosphamide	3454 (28.5%)
Gemcitabine	726 (6.0%)
Fluorouracil	557 (4.6%)
Platinum	8536 (70.4%)
Anthracyclines*	2749 (22.7%)
Taxanes†	5580 (46.0%)

\* Anthracyclines include doxorubicin and epirubicin.

† Taxanes include paclitaxel and docetaxel.

different types of cancer were estimated by excluding SPMs occurring within 1 year after the diagnosis of ovarian cancer to exclude surveillance bias. Univariate and multivariate Cox proportional hazard regression analysis was performed to find out risk factors for SPM development among patients with ovarian cancer. These factors included not only age and comorbidities, but also surgery, chemotherapy, and radiotherapy. To avoid immortal time bias, each treatment modality (eg, surgery, chemotherapy, radiotherapy) after ovarian cancer diagnosis was treated as a time-dependent variable. Multivariate analysis was performed in factors with  $P$  values  $< 0.1$  in univariate analyses.

The data in this study were processed and computed by the Perl programming language (version 5.12.2; Perl Foundation, Walnut, CA). Data linkage and sampling were accomplished by Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA). The statistical analysis was managed by SAS software (version 9.2; SAS Institute Inc, Cary, NC). Statistical significance was defined when  $P < 0.05$ .

## RESULTS

### Characteristics of the Study Population

We identified 13,492 patients diagnosed with ovarian cancer between 1997 and 2010 in the NHIRD's catastrophic illness registry. Of these patients, 406 patients were misclassified, 357 patients were aged  $< 20$  years, and 599 patients had antecedent malignancies; follow-up data were not available for 3 patients. Thus, the final sample consisted of 12,127 patients, with a median age of 50 (interquartile range, 42–61) years at diagnosis. From 1997 to 2011, 56,214 person-years were observed in this cohort. The baseline characteristics of the study cohort are described in Table 1.

**TABLE 2.** Standardized Incidence Ratios According to Age at Diagnosis and Duration of Ovarian Cancer

Characteristics	Total		
	Observed	Expected	SIR (95% CI)
All cancers	707	253.94	2.78 (2.58–3.00)
Age at diagnosis, yr			
20–39	88	10.82	8.13 (6.52–10.02)
40–59	387	116.99	3.31 (2.99–3.65)
60–79	213	108.66	1.96 (1.71–2.24)
≥80	19	17.48	1.09 (0.65–1.70)
Follow-up time after ovarian cancer, yr			
0–1	300	46.89	6.40 (5.69–7.16)
1–5	245	120.31	2.04 (1.79–2.31)
≥5	162	86.75	1.87 (1.59–2.18)

CI = confidence interval; SIR = standardized incidence ratio.

**All Cancers**

During the follow-up period, 707 cancers developed. A significantly increased risk of all cancers (SIR 2.78, 95% CI 2.58–3.00,  $P < 0.001$ ) was found in ovarian cancer patients. Subgroup analysis showed that SIRs for all cancers were highest among patients aged 20–39 years at the time of diagnosis (SIR 8.13, 95% CI 6.52–10.02). Subgroup analysis based on the period of SPM development (0–1, 1–5, and > 5 years) after ovarian cancer diagnosis yielded SIRs of 6.40 (95% CI 5.69–7.16,  $P < 0.001$ ), 2.04 (95% CI 1.79–2.31,  $P < 0.001$ ), and 1.87 (95% CI 1.59–2.18,  $P < 0.001$ ), respectively. The results of these subgroup analyses are summarized in Table 2.

**Specific Cancer Types**

To avoid surveillance bias, SPMs developed within 1 year after the diagnosis of ovarian cancer was excluded. Significantly higher SIRs were observed for cancers of the colon and rectum (2.14, 95% CI 1.65–2.72), lung and mediastinum (1.58, 95% CI 1.09–2.22), breast (1.68, 95% CI 1.36–2.06), cervix (1.65, 95% CI 1.05–2.48), uterus (7.96, 95% CI 6.18–10.09), bladder (3.17, 95% CI 1.73–5.32), and thyroid (2.23, 95% CI 1.34–3.48), as well as leukemia (3.98, 95% CI 1.99–7.12). SIRs for specific cancer types are shown in Table 3.

**Predictors of Cancer Risk**

Univariate Cox proportional hazard analysis showed that age ≥50 years, diabetes mellitus, and dyslipidemia were associated significantly with a higher risk of cancer development. Multivariate analysis showed that age ≥50 years (hazard ratio [HR] 1.60, 95% CI 1.31–1.96,  $P < 0.001$ ) remained an independent predictor of SPM development. SPM risk differed according to ovarian cancer treatment (radiotherapy: HR 2.07, 95% CI 1.51–2.85,  $P < 0.001$ ; chemotherapy: HR 1.27, 95% CI 1.02–1.59,  $P = 0.033$ ). Among chemotherapy agents, fluorouracil was associated with a significantly increased risk of SPM development (HR 5.18, 95% CI 3.66–7.33,  $P < 0.001$ ). These results are itemized in Tables 4 and 5.

**DISCUSSION**

This present study is the first to distinctly demonstrate a significantly increased SIR for metachronous SPM among

**TABLE 3.** Standardized Incidence Ratios for Specific Cancer Types Among Patients With Ovarian Cancer

Cancer Site	Follow-Up > 1 yr		
	Observed	Expected	SIR (95% CI)
All	407	207.05	1.97 (1.78–2.17)
Head and neck	7	6.46	1.08 (0.44–2.23)
Digestive system	100	64.74	1.54 (1.26–1.88)
Esophagus	0	0.78	0.00 (0.00–4.74)
Stomach	11	8.22	1.34 (0.67–2.39)
Colon and rectum, anus	65	30.42	2.14 (1.65–2.72)
Liver and biliary tract	21	21.74	0.97 (0.60–1.48)
Pancreas	3	3.58	0.84 (0.17–2.45)
Lung and mediastinum	33	20.87	1.58 (1.09–2.22)
Bone and soft tissue	3	1.59	1.88 (0.39–5.50)
Skin	7	3.96	1.77 (0.71–3.64)
Breast	93	55.36	1.68 (1.36–2.06)
Genitourinary	114	32.67	3.49 (2.88–4.19)
Cervix	23	13.93	1.65 (1.05–2.48)
Uterus	68	8.55	7.96 (6.18–10.09)
Bladder	14	4.42	3.17 (1.73–5.32)
Kidney	9	5.77	1.56 (0.71–2.96)
Thyroid	19	8.53	2.23 (1.34–3.48)
Hematologic	15	8.70	1.72 (0.96–2.84)
NonHodgkin’s lymphoma	4	4.60	0.87 (0.24–2.22)
Hodgkin’s disease	0	0.16	0.00 (0.00–22.52)
Multiple myeloma	0	1.17	0.00 (0.00–3.15)
Leukemia	11	2.76	3.98 (1.99–7.12)
All others	16	4.17	3.83 (2.19–6.23)

CI = confidence interval; SIR = standardized incidence ratio.

ovarian cancer patients in Asia. Our main findings were: patients with ovarian cancer have significantly increased risk of SPM in the colon and rectum, anus, lung and mediastinum, breast, cervix, uterus, bladder, and thyroid, as well as leukemia; age ≥50 years, radiotherapy, and chemotherapy were independent risk factors for SPM; and among chemotherapeutic agents, fluorouracil significantly increased the risk of SPM.

Several studies have focused on the issue of SPM after ovarian cancer.<sup>5–9,11–21</sup> Most of these studies demonstrated an increased risk of SPM,<sup>5–8,12,14,15,17,18,20</sup> but others did not.<sup>9,11,13</sup> Bergfeldt et al<sup>9</sup> proposed that findings of increased occurrence of secondary primary cancer in patients with ovarian cancer have been biased by misclassification. A study conducted in the UK confirmed the high incidence of synchronous cancer in patients with ovarian cancer, which may also bias estimates of SPM incidence.<sup>14</sup> In addition, most previous studies were single-institute case series; few nationwide or multiple-institute cohort studies have been conducted with reference groups to examine the SIR or relative risk of SPM. Furthermore, recent changes in chemotherapy regimens may also influence the risk of SPM. To avoid surveillance bias, we strictly excluded SPMs occurring within 1 year after ovarian cancer diagnosis. This exclusion may have resulted in bias toward the null, increasing the likelihood that SIRs are insignificant. Nevertheless, the SIR remained significantly higher (1.30, 95% CI 1.23–1.37). Our results are highly credible because our cohort consisted of patients identified by unbiased nationwide selection and reliable diagnostic criteria supported by histological evidence.

**TABLE 4.** Risk Factors for Cancer Development in Patients With Ovarian Cancer (Follow-Up > 1 Yr; n = 10,240)

Variable	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age ≥ 50 yr	1.74 (1.43–2.12)	<0.001	1.60 (1.31–1.96)	<0.001
Comorbidities				
Diabetes mellitus	1.42 (1.08–1.87)	0.014	1.14 (0.85–1.52)	0.374
COPD	1.00 (0.72–1.40)	0.988		
Liver cirrhosis	1.14 (0.59–2.21)	0.701		
Autoimmune diseases	0.96 (0.60–1.55)	0.881		
Dyslipidemia	1.44 (1.09–1.89)	0.010	1.25 (0.95–1.66)	0.115
Chronic kidney disease	1.32 (0.90–1.94)	0.161		
Treatment†				
Chemotherapy	1.42 (1.15–1.77)	0.002	1.27 (1.02–1.59)	0.033
Radiotherapy	2.33 (1.71–3.19)	<0.001	2.07 (1.51–2.85)	<0.001
Surgery	1.12 (0.83–1.49)	0.462		

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

\* All factors with  $P < 0.1$  in univariate analyses were included in the Cox multivariate analysis.

† Treatment was analyzed as a time-dependent covariate in the Cox regression model.

Using the NHI's comprehensive database, we were able to follow almost all patients diagnosed with ovarian cancer in Taiwan during the study period. The present study was the first to show that the SIR for SPM was highest at 0–1 year (these cases were subsequently excluded to avoid surveillance bias), followed by 1–5 and ≥5 years. In a subgroup analysis, we confirmed that patients aged 20–39 years at diagnosis had the highest risk of SPM. This finding implies that thorough examination to detect synchronous cancer should be performed at the time of ovarian cancer diagnosis. Circumspective follow-up is also necessary, especially in young patients.

Our finding of an increased SIR for SPM in this cohort is similar to those of Swiss and UK registry studies.<sup>6,8,12,14,15</sup> An increased risk of colorectal cancer was also reported in a previous study.<sup>12</sup> Several studies have described an increased risk of secondary breast cancer after ovarian cancer, with a focus on invasive forms.<sup>11,13,15</sup> Several possible explanations may be offered for the increased risk of SPM after ovarian cancer. First, an inherent or acquired defect of tumor suppressor

genes or DNA repair genes may induce such cancers.<sup>22–27</sup> Second, these cancers may share underlying lifestyle-related risk factors.<sup>28,29</sup> Third, chemotherapy regimens may be carcinogenic.<sup>30</sup> The occurrence of bladder cancer and leukemia has been attributed to ovarian cancer treatment.<sup>20</sup> Further research is warranted to determine the exact relationships between these factors and the underlying mechanisms.

Our finding that older age was an independent risk factor for SPM after ovarian cancer diagnosis is consistent with the previous findings. Among all comorbidities for which information was available in our database, diabetes mellitus, and dyslipidemia were risk factors in univariate analysis; however, they were not found to be significant in multivariate analysis. In the general population, the overall risks of cancer in patients with diabetes,<sup>31</sup> nonliver malignancies in patients with cirrhosis,<sup>32</sup> and nonpulmonary malignancies in patients with chronic obstructive pulmonary disease (COPD) are higher.<sup>33</sup> Follow-up and clinical decision making should be more aggressive in patients with these risk factors.

**TABLE 5.** Risk Factors for Cancer Development in Patients With Ovarian Cancer (Follow-Up > 1 yr; n = 10,240)

Chemotherapy	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Treatment†				
Cyclophosphamide	1.08 (0.88–1.33)	0.454		
Gemcitabine	2.20 (1.33–3.64)	0.002	1.32 (0.78–2.24)	0.303
Fluorouracil	6.74 (4.87–9.31)	<0.001	5.18 (3.66–7.33)	<0.001
Platinum	1.20 (0.98–1.48)	0.085	0.98 (0.79–1.23)	0.879
Anthracyclines‡	1.62 (1.26–2.07)	0.000	1.19 (0.90–1.57)	0.220
Taxanes§	1.16 (0.94–1.43)	0.179		

CI = confidence interval; HR = hazard ratio.

\* Adjusted for age, diabetes mellitus, dyslipidemia, and radiotherapy.

† Treatment was analyzed as a time-dependent covariate in the Cox regression model.

‡ Anthracyclines include doxorubicin and epirubicin.

§ Taxanes include paclitaxel and docetaxel.

We found that chemotherapy and radiotherapy, considered to be time-dependent variables, increased the risk of SPM. In 1978, Reimer et al<sup>20</sup> proposed that chemotherapy and radiotherapy induced SPMs following ovarian cancer, but treatment regimens and guidelines have changed in the past decades. In the present study, cyclophosphamide, gemcitabine, fluorouracil, and anthracyclines were risk factors SPM after ovarian cancer. Among them, only fluorouracil was an independent risk factor for SPM in multivariate analysis. Fluorouracil was found to be carcinogenic in mice,<sup>34</sup> but evidence for any similar effect in humans is inadequate.<sup>35</sup> 5-fluorouracil (5-FU) is not a global standard chemotherapeutic agent for ovarian cancer. For financial reasons, Taiwan's NHI reimbursement regulations do not necessarily follow global guidelines; 5-FU and its derivatives are considered to be reasonable regimens after recurrence, although a minority of patients (4.6%) receive these regimens. The events were rare but significant. To our knowledge, this study is the first to compare SPM risk among patients receiving different chemotherapy regimens. Further large-scale studies should be conducted to clarify this finding.

This retrospective study has several limitations. First, family history and lifestyle factors, such as exercise, obesity, tobacco use, and alcohol consumption, which were not recorded in the NHI database, are potential confounders. However, some comorbidities potentially associated with such lifestyle factors were found to be independent risk factors for SPM. Second, the disease stage and microscopic features (ie, grade) of ovarian cancer were not documented in the NHI database. Levi et al<sup>8</sup> proposed that the risk of subsequent cancer was higher in patients with invasive ovarian cancer than in those with borderline characteristics. According to treatment consensus in Taiwan, only patients with invasive ovarian cancer received chemotherapy. Most (73.7%) patients in our cohort received chemotherapy, and these cases tended to be invasive. Third, information on histological subtype and genetic mutations, such as the BRCA mutation, was not available in our database. Previous studies have found associations between this mutation and several cancer types.<sup>26,27,36–39</sup> Finally, information on clinical symptoms and detailed laboratory data were not available, preventing determination of the predictive value of specific clinical situations.

In conclusion, our results demonstrate that the risk of SPM is significantly higher among patients with ovarian cancer. Age, chemotherapy, and radiotherapy are independent risk factors for SPM in this population. Among all chemotherapy regimens, fluorouracil-based regimens were independent risk factors. Post-chemotherapy/radiotherapy surveillance, especially of older patients and those who have received fluorouracil regimens, may be crucial for the early detection of SPM.

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