Secondary Primary Malignancy Risk in Patients With Cervical Cancer in Taiwan

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

Patients newly diagnosed with cervical cancer between 1997 and 2011 were identified using Taiwan’s National Health Insurance database. Patients with antecedent malignancies were excluded. Standardized incidence ratios (SIRs) for SPM were calculated by comparing the cancer incidence in the general population. Risk factors for SPM = secondary primary malignancy.

Cervical cancer is the fourth most common cancer in women worldwide, with about 528,000 new cases diagnosed in 2012. Cervical cancer incidence rates are decreasing among women in the United States. However, the incidence of cervical cancer remains high and is a leading cause of death in women in developing countries. Advances in screening, surgery technique, radiotherapy, and chemotherapy have improved survival of cervical cancer. Different treatments for cervical cancer, including radiotherapy (HR 1.41) and chemotherapy (HR 1.27), had different impacts on SPM risk. Carboplatin and fluorouracil independently increased SPM risk in cervical cancer patients. Patients with cervical cancer are at increased risk of SPM development. Age ≥60 years, chemotherapy, and radiotherapy are independent risk factors. Carboptatin and fluorouracil also increased SPM risk independently. Close surveillance of patients at high risk should be considered for the early detection of SPMs.
was based on the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program enrolled 26,290 cervical cancer patients and showed a significantly increased risk in subsequent esophageal cancer, stomach cancer, lung and bronchial cancer, and bladder cancer.⁶,⁷ A Japanese cohort, which enrolled 2167 cervical patients who underwent radiotherapy, showed a small but significant risk of SPMs.⁸ Most of these studies focused on the effect of radiotherapy. Furthermore, few studies have comprehensively coordinated subjects’ medical history and radiation therapy history to evaluate these effects thoroughly. To clarify the incidence of SPMs in cervical cancer, we conducted a nationwide population-based study to examine SPM after the occurrence of cervical cancer.

Taiwan’s National Health Insurance Research Dataset (NHIRD) provides nationwide population data for health research. As all malignancies are registered precisely, the NHIRD is proper for the analysis of SPMs. In addition to patients’ age and sex, the NHIRD provides complete information on comorbidities, which were not simultaneously integrated in most previous studies on cervical cancer. The aim of this study is to compare the overall incidence of SPMs among patients with cervical cancer with the expected incidence in an age-, sex-, and calendar year-matched population using the NHIRD, and to calculate the standardized incidence ratios (SIRs). In addition, we investigated the potential predisposition of patients with cervical cancer to SPMs with respect to chemotherapy, radiotherapy, and comorbidities. The different impacts to risk of SPMs in individual chemotherapy agents were also analyzed.

METHODS

Data Sources
The universal National Health Insurance (NHI) program in Taiwan was initiated in 1995. It provides comprehensive medical care to all of Taiwan’s residents, with a coverage rate of more than 99%.³ The program provides coverage for outpatient, emergency, inpatient, dental, and traditional Chinese medicine services, as well as prescription drugs.

Based on NHIRD, we also introduced the Registry of Catastrophic Illness, which provides comprehensive information on NHI enrollment and health care resource provisions for patients with serious diseases, whose medical copayments are exempted under the NHI program. The NHIRD integrates several NHI databases, which consists of claims data, NHI enrollment files, and the drug prescription registry. Cervical cancer and all other types of malignancies are categorized as catastrophic illnesses. All information that would potentially identify individual patients is encrypted. The data are confidential, as mandated by the Bureau of NHI and the National Health Research Institutes. 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
Newly diagnosed cases of cervical cancer (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 181) during the period January 1, 1997 to December 31, 2011 were identified and enrolled from the Registry of Catastrophic Illness. Patients diagnosed with cervical cancer before January 1, 1997 were not enrolled. Patients aged under 20 at the time of diagnosis and those who had antecedent malignancies were excluded. The main dependent variable in our study was development of SPMs. To avoid misclassification, ill-defined or unspecified cancers were not considered as SPMs. For subjects identified using the Registry of Catastrophic Illness, histological evidence for the malignant diagnosis was required. Every patient was followed until the occurrence of an SPM, death, dropout from the NHI program, or the end of 2011. Information on comorbidities, radiotherapy, and chemotherapeutic agents was also collected from NHIRD for further analysis.

Statistical Analysis
SIRs, defined as the observed number of cancer occurrences divided by the expected number of such occurrences, were used to determine the risk of SPMs in our study cohort. The expected number of cancer occurrences was calculated simply by multiplying the cancer incidence in the general population (retrieved from Taiwan’s National Cancer Registry) by the number of patients in the corresponding age group in the study cohort. Each group was stratified according to calendar year in 5-year intervals by the corresponding stratum-specific person-time accrued in the cohort. Ninety-five percent confidence intervals (CIs) of SIRs were estimated by the assumption that the observed number of cancer occurrences followed a Poisson probability distribution. We defined SIRs for subgroups based on age. A subgroup analysis stratified by the period of SPM development was performed to avoid surveillance bias. For the same reason, SIRs for different types of cancer were estimated by excluding SPMs occurring within 1 year after the diagnosis of cervical cancer. Risk factors for SPM development among patients with cervical cancer were analyzed using univariate and multivariate Cox proportional hazard models. These factors included not only age and comorbidities but also surgery, radiotherapy, and chemotherapy. Factors with P values <0.1 in the univariate analysis were entered into the Cox multivariate analysis.

Data were extracted and computed using the Perl programming language (version 5.12.2; Perl Foundation, Walnut, CA). Data linkage, processing, and sampling were conducted using Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA). SAS software (version 9.2; SAS Institute Inc, Cary, NC) was used for all statistical analyses. Statistical significance was defined as P <0.05.

RESULTS

Characteristics of the Study Population
We identified 36,399 patients diagnosed with cervical cancer between 1997 and 2011 in the NHIRD’s Catastrophic Illness Registry. Of these, 296 patients were misclassified, 8 patients were aged <20, and 920 patients had antecedent malignancies. Thus, the final sample consisted of 35,175 patients, with a median age of 55.32 (interquartile range, 45.49–67.33) at diagnosis. The detail of patients’ enrolment is demonstrated in Figure 1. Overall, this cohort was observed for 223,062 person-years from 1997 to 2011. The characteristics of the cohort are shown in Table 1.

All Cancers
During the observation period, 2004 cancers developed. Compared with the general population, patients with cervical cancer had a significantly increased risk of all cancers (SIR
1.56, 95% CI 1.50–1.63, \( P < 0.001 \). Subgroup analysis showed that SIRs for all cancers were highest among patients aged 20 to 39 at the time of diagnosis (SIR 3.99, 95% CI 3.07–5.09, \( P < 0.001 \)). Subgroup analysis based on the period of SPM development (0–1, 1–5, 5–10, and \( \geq 10 \) yr) after cervical cancer diagnosis yielded SIRs of 2.59 (95% CI 2.35–2.85, \( P < 0.001 \)), 1.34 (95% CI 1.24–1.45, \( P < 0.001 \)), 1.51 (95% CI 1.40–1.63, \( P < 0.001 \)), and 1.37 (95% CI 1.21–1.56, \( P < 0.001 \)), respectively. The results of these subgroup analyses are summarized in Table 2. The cumulative incidence of secondary primary malignancies in patients with cervical cancer is demonstrated in Figure 2.

### Specific Cancer Types

After excluding SPMs developed within 1 year after diagnosis of cervical cancer, significantly higher SIRs were observed for cancers of the esophagus (2.05, 95% CI 1.02–3.67, \( P = 0.043 \)), stomach (1.38, 95% CI 1.09–1.72, \( P = 0.009 \)), colon and rectum (1.36, 95% CI 1.21–1.54, \( P < 0.001 \)), lung and mediastinum (2.28, 95% CI 2.03–2.55, \( P < 0.001 \)), bone and soft tissue (2.23, 95% CI 1.34–3.48, \( P = 0.003 \)), uterus (3.76, 95% CI 3.16–4.44, \( P < 0.001 \)), bladder (2.26, 95% CI 1.76–2.86, \( P < 0.001 \)), and kidneys (1.41, 95% CI 1.06–1.84, \( P = 0.018 \)). SIRs for specific cancer types are shown in Table 3.

### Predictors of Cancer Risk

Univariate Cox proportional hazard analysis showed that age \( \geq 60 \), diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease, liver cirrhosis, autoimmune disease, and dyslipidemia were associated significantly with a higher risk of cancer development. Multivariate analysis showed that age \( \geq 60 \) (hazard ratio [HR] 1.59, 95% CI 1.43–1.77, \( P < 0.001 \)) remained an independent predictor of SPM development. Furthermore, chemotherapy (hazard ratio [HR] 1.41, 95% CI 1.25–1.59, \( P < 0.001 \)) and radiotherapy (hazard ratio [HR] 1.27, 95% CI 1.14–1.43, \( P < 0.001 \)) were independent risk factors in the multivariate analysis. We also analyzed the impact of common chemotherapy agents on SPM occurrence among cervical cancer patients. Multivariate analysis showed that chemotherapy agents with fluorouracil (HR) 1.51 95% CI 1.22–1.87, \( P < 0.001 \) and carboplatin (HR) 1.58 95% CI 1.20–2.07, \( P = 0.001 \) independently increased risk of SPM under the multivariate analysis. These results are itemized in Tables 4 and 5.

### Table 1. Characteristics of Cervical Cancer Patients

| Patients                                |
|-----------------------------------------|
| No. of patients                         | 35,175                                  |
| Person-years at risk                    | 223,062                                 |
| Median follow-up, yr (interquartile range) | 5.70 (1.96–10.58)                       |
| Median age, yr (interquartile range)    | 55.32 (45.49–67.33)                     |
| Age at diagnosis, yr                    |                                          |
| 20–39                                   | 4238                                    |
| 40–59                                   | 16,831                                  |
| 60–79                                   | 12,024                                  |
| \( \geq 80 \)                            | 2082                                    |
| Comorbidities (%)                       |                                          |
| Diabetes mellitus                       | 5668 (16.1)                             |
| Hypertension                            | 10,509 (29.9)                           |
| Chronic obstructive pulmonary disease   | 4298 (12.2)                             |
| Chronic kidney disease                  | 2862 (8.1)                              |
| Liver cirrhosis                         | 387 (1.1)                               |
| Autoimmune diseases                     | 1866 (5.3)                              |
| Dyslipidemia                            | 5377 (15.3)                             |
| Treatment (%)                           |                                          |
| Surgery                                 | 20,778 (59.1)                           |
| Chemotherapy                            | 13,291 (37.8)                           |
| Cisplatin                               | 11,327 (32.2)                           |
| Fluorouracil                            | 3037 (8.6)                              |
| Carboplatin                             | 2312 (6.6)                              |
| Ifosfamide                              | 1800 (5.1)                              |
| Topotecan                               | 580 (1.7)                               |
| Radiotherapy                            | 19,106 (54.3)                           |

COPD = chronic obstructive pulmonary disease.
TABLE 2. Standardized Incidence Ratios According to Sex, Age at Diagnosis, and Follow-Up Time

| Characteristics | Observed | Expected | SIR (95% CI) | P Value |
|-----------------|----------|----------|--------------|---------|
| All cancers     | 2004     | 1281.93  | 1.56 (1.50–1.63)* | <0.001  |
| Age at diagnosis|          |          |              |         |
| 20–39           | 64       | 16.04    | 3.99 (3.07–5.09)* | <0.001  |
| 40–59           | 752      | 393.65   | 1.91 (1.78–2.05)* | <0.001  |
| 60–79           | 973      | 699.61   | 1.39 (1.30–1.48)* | <0.001  |
| ≥80             | 215      | 172.64   | 1.25 (1.08–1.42)* | 0.002   |
| Follow-up time after cervical cancer diagnosis, in yr |          |          |              |         |
| 0–1             | 419      | 161.69   | 2.59 (2.35–2.85)* | <0.001  |
| 1–5             | 675      | 503.17   | 1.34 (1.24–1.45)* | <0.001  |
| 5–10            | 670      | 442.45   | 1.51 (1.40–1.63)* | <0.001  |
| ≥10             | 240      | 174.63   | 1.37 (1.21–1.56)* | <0.001  |

CI = confidence interval; SIR = standardized incidence ratio.

* P < 0.05.

DISCUSSION

Our study is a nationwide population-based study to clearly demonstrate significantly increased SIRs for metachronous SPMs among patients with cervical cancer. The main findings were that patients with cervical cancer have significantly increased risk of SPMs in the esophagus, stomach, colon and rectum, lung and mediastinum, bone and soft tissue, uterus, bladder, kidneys; SIRs for all cancers were highest among patients aged 20 to 39 at the time of diagnosis; independent risk factors for SPMs include age ≥60, hypertension, chemotherapy, and radiotherapy; the chemotherapy agents carboplatin and fluorouracil are independent risk factors for SPMs in cervical cancer patients.

Several studies have discussed the issue of SPMs after cervical cancer.2–5,10–23 Most of these studies emphasized the effects of radiotherapy and the majority focused on Western patients. Most Asian studies were conducted in or by single institutes and had limited populations.4,8,25,30,31 A study published in 2012 based on the Taiwan Cancer Registry that enrolled 52,972 patients also found increased SIRs in patients with cervical cancer.4 However, only the age of patients, registry date, and sites of cancer were analyzed. In the present study, we enrolled 35,175 cervical cancer patients and not only obtained the full claims data but also corroborated with the cancer registry to confirm the results. By using the NHIIRD, we can take patients’ comorbidities and their treatment modalities into consideration. Our results are convincing because our cohort included patients identified by unbiased nationwide selection and reliable diagnostic criteria supported by pathological evidence.

Although our study demonstrated that SIRs for SPMs were highest at 0 to 1 years, the higher SIRs might be confounded by surveillance bias. After excluding SPMs at 0 to 1 years, SIRs showed no difference between those of the 1 to 5, 5 to 10, and ≥10 groups when examined using a Pearson χ² test (P = 0.476). In the subgroup analysis, we found that patients aged 20 to 39 at diagnosis had the highest SIRs of SPMs. The SEER study reported a similar result.7 Though the absolute risk of SPMs in this age group is modest when compared with those of the elderly, they are at a much higher risk than people without cervical cancer in the same age group. These findings imply that thorough examination is warranted to detect synchronous cancers when cervical cancer is diagnosed. Cautious follow-up is also necessary even after 10 years.

The increased risk of SPMs in cervical cancer patients we found was consistent with most previous studies.2–5,10–23,30,32 Boice et al conducted an international collaborative study that enrolled 182,040 patients from 15 cancer registries in 8 countries and reported that a 9% excess of secondary cancers (5146 observed versus 4736 expected) had occurred 1 or more years after treatment.5,13 Chen et al reported a significantly greater SIR (1.36) of SPM in cervical cancer patients in the Taiwan Cancer Registry.7 Other studies highlighted an increased risk of gastrointestinal cancer after cervical cancer.10,12,13 Some of these studies observed the correlation of secondary primary malignancies with human papillomavirus (HPV) and tobacco use.6,7 We found an increased SIR for SPMs in the esophagus, stomach, colon and rectum, anus, lungs and mediastinum, bones and soft tissue, uterus, bladder, and kidneys.

Several possible etiologies may be applied for the increased risk of SPMs after cervical cancer. First, cervical cancer is a human papillomavirus (HPV)-associated cancer.33 Patients with cervical cancer share the risk with other HPV-associated cancers, such as anal cancer, oropharyngeal cancer, and vaginal cancer.34,35 Second, patients of some cancers may have socioeconomic status and some lifestyle-related risk
factors in common, such as smoking and sexual activity. Third, treatment modality, such as chemotherapy or radiotherapy, may induce SPMs. Further research is needed to determine the possible relationships between these factors and to find the underlying mechanisms.

Increased age was found to be an independent risk factor for SPM after the diagnosis of cervical cancer. Additionally, none of the comorbidities available in our database were independent risk factors for SPMs in cervical cancer patients. However, radiotherapy and chemotherapy, which were considered to be time-dependent factors in common, such as smoking and sexual activity. Further research is needed to determine the possible relationships between these factors and to find the underlying mechanisms.

TABLE 3. Standardized Incidence Ratios for Cancer Subtypes Among Cervical Cancer Patients (Follow-Up More Than 1 Yr)

| Site of Cancer                        | Observed | Expected | SIR (95% CI) | P Value |
|---------------------------------------|----------|----------|--------------|---------|
| All cancers                           | 1585     | 1120.24  | 1.41 (1.35–1.49)* | <0.001  |
| Head and neck                         | 38       | 33.58    | 1.13 (0.80–1.55) | 0.489   |
| Digestive                             | 529      | 433.65   | 1.22 (1.12–1.33)* | <0.001  |
| Esophagus                             | 11       | 5.36     | 2.05 (1.02–3.67)* | 0.043   |
| Stomach                               | 77       | 55.90    | 1.38 (1.09–1.72)* | 0.009   |
| Colon and rectum, anus                | 268      | 196.55   | 1.36 (1.21–1.54)* | <0.001  |
| Liver and biliary tract               | 153      | 151.02   | 1.01 (0.86–1.19) | 0.894   |
| Pancreas                              | 20       | 24.82    | 0.81 (0.49–1.24) | 0.390   |
| Lung and mediastinum                  | 306      | 134.03   | 2.28 (2.03–2.55)* | <0.001  |
| Bone and soft tissue                  | 19       | 8.53     | 2.23 (1.34–3.48)* | 0.003   |
| Skin                                  | 36       | 28.73    | 1.25 (0.88–1.73) | 0.212   |
| Breast                                | 232      | 243.44   | 0.95 (0.83–1.08) | 0.487   |
| Genitourinary                         | 299      | 136.55   | 2.19 (1.95–2.45)* | <0.001  |
| Uterus                                | 138      | 36.72    | 3.76 (3.16–4.44)* | <0.001  |
| Ovaries                               | 36       | 29.96    | 1.20 (0.84–1.66) | 0.311   |
| Bladder                               | 70       | 30.93    | 2.26 (1.76–2.86)* | <0.001  |
| Kidneys                               | 55       | 38.94    | 1.41 (1.06–1.84)* | 0.018   |
| Urinary system thyroid                | 33       | 33.45    | 0.99 (0.68–1.39) | 0.970   |
| Hematologic                           | 68       | 51.15    | 1.33 (1.03–1.69)* | 0.028   |
| Non-Hodgkin’s lymphoma                | 35       | 26.91    | 1.30 (0.91–1.81) | 0.152   |
| Hodgkin’s disease                     | 0        | 0.66     | 0.00 (0.00–5.57) | 0.966   |
| Multiple myeloma                      | 11       | 7.63     | 1.44 (0.72–2.58) | 0.298   |
| Leukemia                              | 22       | 15.95    | 1.38 (0.86–2.09) | 0.174   |
| Others                                | 25       | 17.13    | 1.46 (0.94–2.15) | 0.087   |

CI = confidence interval; N/A = not applicable; SIR = standardized incidence ratio.

TABLE 4. Risk Factors for Cancer Development Among Cervical Cancer Patients (Follow-Up More Than 1 Yr) (n=30,149)

| Variables                             | Univariate Analysis | Multivariate Analysis |
|---------------------------------------|---------------------|-----------------------|
|                                       | HR (95% CI)         | P Value               | HR (95% CI)         | P Value   |
| Age ≥ 60                              | 1.72 (1.56–1.90)    | <0.001                | 1.59 (1.43–1.77)    | <0.001    |
| Comorbidities                         |                     |                       |                      |           |
| Diabetes mellitus                     | 1.42 (1.23–1.64)    | <0.001                | 1.12 (0.96–1.31)    | 0.154     |
| COPD                                  | 1.33 (1.13–1.57)    | 0.001                 | 1.06 (0.90–1.26)    | 0.484     |
| Chronic kidney disease                | 1.46 (1.18–1.80)    | <0.001                | 1.19 (0.96–1.48)    | 0.119     |
| Liver cirrhosis                       | 1.84 (1.09–3.11)    | 0.023                 | 1.44 (0.84–2.44)    | 0.182     |
| Autoimmune diseases                   | 1.29 (1.01–1.65)    | 0.040                 | 1.09 (0.85–1.40)    | 0.504     |
| Dyslipidemia                          | 1.37 (1.18–1.59)    | <0.001                | 1.08 (0.92–1.28)    | 0.340     |
| Treatment†                            | 0.74 (0.67–0.82)    | <0.001                | 0.94 (0.84–1.04)    | 0.229     |
| Surgery                               | 1.54 (1.39–1.71)    | <0.001                | 1.41 (1.25–1.59)    | <0.001    |
| Chemotherapy                          | 1.63 (1.48–1.80)    | <0.001                | 1.27 (1.14–1.43)    | <0.001    |

COPD = chronic obstructive pulmonary disease.

All factors with P < 0.1 in the univariate analysis were included in the Cox multivariate analysis.

Treatment was analyzed as a time-dependent covariate in the Cox regression model.
TABLE 5. Risk Factors for Cancer Development Among Cervical Cancer Patients (Follow-Up More Than 1 Yr) (n = 30,149)

| Chemotherapy Variables | Univariate Analysis | Multivariate Analysis* |
|------------------------|---------------------|------------------------|
|                        | HR (95% CI)         | P Value                | HR (95% CI)         | P Value |
| Treatment†             |                     |                       |                       |         |
| Cisplatin              | 1.20 (1.07–1.35)    | 0.003                  | 0.91 (0.79–1.05)     | 0.204   |
| Fluorouracil           | 1.67 (1.38–2.02)    | <0.001                 | 1.51 (1.22–1.87)     | <0.001  |
| Carboplatin            | 1.81 (1.39–2.35)    | <0.001                 | 1.58 (1.20–2.07)     | 0.001   |
| Ifosfamide             | 1.12 (0.82–1.54)    | 0.464                  |                       |         |
| Topotecan              | 2.27 (1.02–5.05)    | 0.045                  | 1.60 (0.71–3.61)     | 0.260   |

CI = confidence interval; HR = hazard ratio.
* All factors with P < 0.1 in the univariate analysis shown in Table 4 were included in the Cox multivariate analysis.
† Treatment was analyzed as a time-dependent covariate in the Cox regression model.
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