Risk of Nongenitourinary Cancers in Patients With Spinal Cord Injury

A Population-based Cohort Study

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Abstract: Little information is available regarding the risk of non-genitourinary (GU) cancers in patients with spinal cord injury (SCI). The authors conducted a nationwide population-based study to investigate whether a higher risk of non-GU cancer is seen among patients with SCI.

Data retrieved from the National Health Insurance Research Database of Taiwan were used in this study. A total of 41,900 patients diagnosed with SCI between 2000 and 2011 were identified from the National Health Insurance Research Database and comprised the SCI cohort. Each of these patients was randomly frequency matched with 4 people from the general population (without SCI) according to age, sex, comorbidities, and index year. Cox proportional hazards regression analysis was used to calculate adjusted hazard ratios and 95% confidence intervals and determine how SCI affected non-GU cancer risk.

No significant difference in overall non-GU cancer risk was observed between the SCI and control groups. The patients with SCI exhibited a significantly higher risk of developing esophageal, liver, and hematologic malignancies compared with those without SCI. By contrast, the SCI cohort had a significantly lower risk of colorectal cancer compared with the non-SCI cohort (adjusted hazard ratio = 0.80, 95% confidence interval = 0.69–0.93). Additional stratified analyses by sex, age, and follow-up duration revealed various correlations between SCI and non-GU cancer risk.

The patients with SCI exhibited higher risk of esophageal, liver, and hematologic malignancies but a lower risk of colorectal cancer compared with those without SCI. The diverse patterns of cancer risk among the patients with SCI may be related to the complications of chronic SCI.

INTRODUCTION

Spinal cord injury (SCI) is an insult to the spinal cord that results in lost or impaired function causing reduced mobility or feeling below the level of injury. Common causes of SCI are trauma, disease, and degeneration. Up to 90% of cases are because of trauma. The reported annual incidence of SCI ranges between 10.4 and 83 per million inhabitants worldwide and between 15 and 55 per million in North America.1–3 The incidence in Taiwan is much higher, at 150 per million according to a nationwide health insurance database.4 With improvements in the technology used for the clinical care, treatment, and follow-up of individuals with SCI, the life expectancy of these patients has been significantly increased and approached that of the general population.5 Consequently, most patients with SCI are likely to encounter aging-related problems such as cancer.6

The relationship between cancer risk and SCI has been explored for decades, but most research has focused on genitourinary (GU) tract cancers. Studies have suggested a lower prevalence of prostate cancer in patients with SCI.7–9 Reports, however, have also noted an increased risk of bladder cancer in patients with SCI.
patients with SCI. \textsuperscript{10,11} We previously found that patients with SCI had a lower risk of prostate cancer compared with people without SCI, but that the risk of bladder cancer did not differ between people with and without SCI. \textsuperscript{12}

Scant information is available regarding the risk of non-GU cancers in patients with SCI. Studies investigating colonscopic lesions in patients with SCI have reported inconsistent results. \textsuperscript{13–15} In a study of veterans disabled by myelopathy, Frisble et al found a 2- to 6-fold increase in the age-adjusted incidence of colorectal carcinoma in males with myelopathy compared with the general male population. \textsuperscript{16} Spinal cord injury changes body composition, metabolism, and hormonal regulation over time \textsuperscript{17} and can cause chronic complications, several of which have been suggested to be associated with some cancer types; these complications include osteoporosis, metabolic syndrome, and venous thromboembolism (VTE). \textsuperscript{17–22}

To our knowledge, no large-scale population-based study has evaluated how SCI may affect the development of non-GU cancers. This study aimed to determine whether non-GU cancer risk was associated with SCI in Taiwan. A retrospective cohort design was adopted to analyze the database of the National Health Insurance program. We hypothesized that the risk of certain non-GU cancers may be increased among patients with SCI.

MATERIALS AND METHODS

Data Source

The data used in this study were obtained from the National Health Insurance Research Database (NHIRD) and covered the period from January 1, 2000 to December 31, 2011. The NHIRD, released by the National Health Research Institutes (NHRI) for research purposes, is a nationwide population-based claims database of the Taiwan NHI program, which was implemented on March 1, 1995 and covers more than 23 million people, representing approximately 99% of the Taiwan population. \textsuperscript{23} The NHIRD contains all reimbursement claims data, including inpatient and outpatient medical claims, hospital information, and patient demographic characteristics. Before releasing the database, the National Health Research Institute scrabbles all personal information and provides an anonymous number for each insured person for linking with their claims data. The current study was approved by the Institutional Review Board of China Medical University and Hospital (CMUH104-REC2-115). The diagnoses in the NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Sampled Patients

We identified adult patients newly diagnosed with SCI (ICD-9-CM codes 806 and 952; \(N = 45,692\)) between 2000 and 2010. The index date of SCI was the date of initial SCI admission diagnosis. Patients with a history of cancer (ICD-9-CM codes 140–195 and 200–208; except metastatic) or until the subject was censored because of loss to follow-up, death, withdrawal from insurance, or the end of follow-up on December 31, 2011. Cancers monitored for included over cancer (\(N = 9258\)), head and neck cancer (ICD-9-CM codes 140–149 and 161; \(N = 950\)), esophageal cancer (ICD-9-CM code 150; \(N = 240\)), stomach cancer (ICD-9-CM code 151; \(N = 458\)), colorectal cancer (ICD-9-CM codes 153 and 154; \(N = 1377\)), liver cancer (ICD-9-CM code 155; \(N = 1543\)), pancreatic cancer (ICD-9-CM code 157; \(N = 179\)), lung cancer (ICD-9-CM code 162; \(N = 1247\)), skin cancer (ICD-9-CM code 173; \(N = 176\)), female breast cancer (ICD-9-CM code 174; \(N = 498\)), uterus cancer (ICD-9-CM codes 180–184; \(N = 338\)), brain cancer (ICD-9 code 191; \(N = 76\)), thyroid cancer (ICD-9 code 193; \(N = 119\)), hematologic malignancy (ICD-9 codes 200–208; \(N = 433\)), and others (\(N = 1624\)).

Statistical Analysis

A \(\chi^2\) test and Student \(t\) test were used to evaluate the allocation of categorical and continuous variables, respectively, between the SCI and non-SCI cohorts. Follow-up person-years were calculated for assessing incidence density rates of cancer. Univariate and multivariate Cox proportional hazards analyses were conducted to investigate the association between SCI and the risk of developing cancer over time. The multivariate models were simultaneously adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke. All statistical analyses were performed using the SAS package (Version 9.4 for Windows; SAS institute, Inc., Cary, NC). A 2-tailed \(P\) value lower than .05 was considered significant.

RESULTS

Table 1 presents the demographic and comorbidity information of the patients. The distribution of sex, age, and comorbidities were similar in both cohorts. More male patients were present in our study, and almost half of the patients were aged younger than 50 years (approximate mean age: 52 year). The mean follow-up times were 5.65 years [standard deviation (SD) = 3.41] and 6 years (SD = 3.24) for the SCI and non-SCI cohorts, respectively (data not shown). The overall incidence of non-GU cancer was not significantly higher in the SCI cohort than it was in the non-SCI cohort (7.40 versus 7.47 per 1000 person-years), exhibiting an adjusted hazard ratio (aHR) of 1.04 [95% confidence interval (CI) = 0.99–1.09] (Table 2). The patients with SCI had a significantly higher risk of hematologic malignancy, esophageal cancer, and liver cancer than did the comparison cohort (aHR = 1.32, 95% CI = 1.06–1.65; aHR = 1.45, 95% CI = 1.08–1.95; and aHR = 1.22, 95% CI = 1.08–1.38, respectively). The aHR for colorectal cancer was 0.80-fold lower for the patients with SCI (95% CI = 0.69–0.93). Compared with the male patients without SCI, those with SCI exhibited a significantly higher risk of esophageal cancer and a significantly lower risk of colorectal cancer (Table 3). Compared with the female patients without SCI, those with SCI exhibited a significantly higher risk of hematologic malignancy
and stroke.

TABLE 1. Demographic Characteristics and Comorbidities in Patients With And Without Spinal Cord Injury

| Variable            | No          | Yes         | P Value |
|---------------------|-------------|-------------|---------|
| Sex                 | N = 167,408 | N = 41,900  |         |
| Female              | N (%)       | N (%)       | 0.96    |
| Male                | 61,277 (36.6) | 15,343 (36.6) |         |
| Age, mean (SD)      | 51.8 (18.4) | 52.2 (18.2) | 0.001*  |
| Stratify age <49    | 79,210 (47.3) | 19,820 (47.3) | 0.99    |
| 50–65               | 41,031 (24.5) | 10,265 (24.5) |         |
| 65+                 | 47,167 (28.2) | 11,815 (28.2) |         |
| Comorbidity         |             |             |         |
| Diabetes            | 20,509 (12.3) | 5155 (12.3) | 0.77    |
| Hypertension        | 32,053 (19.2) | 8033 (19.2) | 0.91    |
| Hyperlipidemia      | 7704 (4.60)  | 1952 (4.66) | 0.62    |
| COPD                | 8620 (5.15)  | 2185 (5.21) | 0.59    |
| Heart failure       | 4993 (2.98)  | 1274 (3.04) | 0.53    |
| CAD                 | 13,820 (8.26) | 3480 (8.24) | 0.74    |
| Stroke              | 12,526 (7.48) | 3159 (7.54) | 0.69    |

χ² test. COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease
* 2-sample t test.

and liver cancer, but also a significantly lower risk of colorectal cancer. Among the patients aged ≤49 years, those with SCI had a significantly higher risk of all cancer, esophageal cancer, and liver cancer compared with those without SCI (Table 4). Among the patients aged ≥50 years, those with SCI had a significantly higher risk of hematologic malignancy and a significantly lower risk of colorectal cancer compared with those without SCI.

Among the patients with a follow-up duration ≤5 years, those with SCI exhibited a significantly higher risk of hematologic malignancy and liver cancer and had a significantly lower risk of colorectal cancer compared with the patients without SCI (Table 5). Among the patients with a follow-up duration >5 years, those with SCI, however, had a significantly higher risk of esophageal cancer compared with those without SCI.

DISCUSSION

Our study revealed no significant difference in overall non-GU cancer risk between the SCI and control groups. Individual cancer risk analysis revealed that patients with SCI exhibited a significantly higher risk of esophageal, liver, and hematologic malignancies. By contrast, a significantly lower risk of colorectal cancer was found in the SCI cohort. Analyses stratified by sex, age, and follow-up duration demonstrated various correlations between SCI and non-GU cancer risk.

Few studies have evaluated non-GU cancer risk among patients with SCI. Most related data are limited to colorectal cancer. In this study, a significantly lower risk of colorectal cancer was found in the SCI group compared with the control group. This result differs from that of Frisbie et al, who reviewed the records of 1023 veterans disabled by myelopathy and found that the age-adjusted incidence rates in the sixth to ninth decades of age were 2 to 6 times larger than the highest reported rates for the general male population (P < 0.05).16 Morris et al conducted a case-control study in Australia and

TABLE 2. Comparison of Incidence and Hazard Ratio of Cancer Types According to Spinal Cord Injury Status

| Cancer (ICD-9-CM)       | SCI Case | Rate^ | Control Case | Rate^ | Crude HR (95% CI) | Adjusted HR† (95% CI) |
|-------------------------|----------|-------|--------------|-------|------------------|----------------------|
| All                     | 1751     | 7.40  | 7507         | 7.47  | 0.99 (0.94, 1.04) | 1.04 (0.99, 1.09)    |
| Hematologic malignancy  | 99       | 0.42  | 334          | 0.33  | 1.26 (1.01, 1.57) | 1.32 (1.06, 1.65)    |
| Head and neck           | 196      | 0.83  | 754          | 0.75  | 1.10 (0.94, 1.29) | 1.14 (0.97, 1.33)    |
| Esophageal cancer       | 59       | 0.25  | 181          | 0.18  | 1.38 (1.03, 1.86) | 1.45 (1.08, 1.95)    |
| Stomach cancer          | 95       | 0.40  | 363          | 0.36  | 1.11 (0.89, 1.39) | 1.19 (0.95, 1.50)    |
| Colorectal cancer       | 208      | 0.88  | 1169         | 1.16  | 0.76 (0.65, 0.88) | 0.80 (0.69, 0.93)    |
| Liver cancer            | 331      | 1.40  | 1212         | 1.21  | 1.16 (1.03, 1.31) | 1.22 (1.08, 1.38)    |
| Pancreas cancer         | 38       | 0.16  | 141          | 0.14  | 1.14 (0.80, 1.64) | 1.21 (0.85, 1.74)    |
| Lung(162)               | 241      | 1.02  | 1006         | 1.00  | 1.02 (0.88, 1.17) | 1.09 (0.95, 1.25)    |
| Skin (173)              | 31       | 0.13  | 145          | 0.14  | 0.91 (0.62, 1.34) | 0.97 (0.66, 1.44)    |
| Female breast(174)      | 86       | 0.96  | 412          | 1.11  | 0.87 (0.69, 1.10) | 0.87 (0.69, 1.10)    |
| Uterus(180–184)         | 59       | 0.66  | 279          | 0.75  | 0.88 (0.66, 1.16) | 0.89 (0.67, 1.18)    |
| Breast cancer           | 15       | 0.06  | 61           | 0.06  | 1.04 (0.59, 1.83) | 1.06 (0.61, 1.87)    |
| Thyroid cancer          | 18       | 0.08  | 101          | 0.10  | 0.76 (0.46, 1.25) | 0.76 (0.46, 1.25)    |
| Others                  | 275      | 1.16  | 1349         | 1.34  | 0.87 (0.76, 0.99) | 0.91 (0.80, 1.04)    |

CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, SCI = spinal cord injury.

* P < 0.05
** P < 0.01.
*** P < 0.001.
† Adjusted HR: multivariate analysis, including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.
^ Rate = incidence rate, per 1000 person-years.Crude HR = relative HR.
found that the patients with SCI had the same risk of malignancy that the general population did.\(^{24}\) In a study of colonoscopic lesions in patients with SCI, Han et al found no difference in cancer detection between an SCI and control group; inflammatory bowel disease, which is a risk factor for cancer, was more common in the SCI group, but not significantly so (\(P = 0.06\)).\(^{14}\)

The conflicting results between our study and previous reports may be partially because of less frequent colonoscopy screenings in the SCI group than in the control group. Because of the inconvenience and relative difficulty of the bowel preparation process necessary for the invasive procedure, patients with SCI receive significantly fewer colonoscopy screenings than does the general population, according to a self-report survey.\(^{25,26}\)

Furthermore, considering several complications of SCI suggested as being related to cancer risk, we expected that a possible association may exist between non-GU cancer and SCI. Osteoporosis is a common consequence of SCI and occurs in almost every patient with SCI. Although the mechanism of this relationship remains unclear, a commonly suggested reason relates to the mechanical unloading of the paralyzed limbs and vascular dysfunction below the level of injury.\(^{18,27}\) Studies examining whether osteoporosis increases cancer risk have yielded inconsistent results.\(^{28–30}\) In a cohort of 23,935 people with osteoporosis, McGlynn et al found a significantly lower risk of colorectal cancer among the female patients compared with the general female population, particularly in the \(\geq 70\) years age group.\(^{30}\) If the cancer risk of patients with osteoporosis can partially reflect that of patients with SCI, then their results are consistent with ours. Our data showed that both male and female patients with SCI had a significantly lower risk of colorectal cancer compared with their counterparts, and the difference was greater for women.

| Variable (ICD-9-CM) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
|---------------------|----------------------|----------------------|
| All                 | 1 (Reference) 1.06 (0.99, 1.13) | 1 (Reference) 1.01 (0.93, 1.11) |
| Hematologic malignancy (200–208) | 1 (Reference) 1.26 (0.95, 1.69) | 1 (Reference) 1.43 (1.00, 2.03) |
| Esophagus cancer (150) | 1 (Reference) 1.45 (1.08, 1.97)* | 1 (Reference) 1.43 (0.39, 5.28) |
| Colorectal cancer (153–154) | 1 (Reference) 0.83 (0.69, 0.99) | 1 (Reference) 0.76 (0.59, 0.96)* |
| Liver cancer (155) | 1 (Reference) 1.15 (1.00, 1.33) | 1 (Reference) 1.38 (1.11, 1.72)** |

**CAD** = coronary artery disease, **CI** = confidence interval, **COPD** = chronic obstructive pulmonary disease, **HR** = hazard ratio, **ICD-9-CM** = International Classification of Diseases Ninth Revision Clinical Modification, **SCI** = spinal cord injury.

*\(P < 0.05\).

**\(P < 0.01\).

***\(P < 0.001\).

\(^{1}\)Adjusted HR: multivariate analysis, including age and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.

**TABLE 3.** Cox Model With Hazard Ratio and 95% confidence intervals Of Cancer Types Associated With Spinal Cord Injury, Stratified by Sex

| Variable (ICD-9-CM) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
|---------------------|----------------------|----------------------|
| All                 | 1 (Reference) 1.24 (1.11, 1.40)** | 1 (Reference) 0.98 (0.93, 1.04) |
| Hematologic malignancy (200–208) | 1 (Reference) 0.87 (0.47, 1.63) | 1 (Reference) 1.41 (1.11, 1.79)** |
| Esophagus cancer (150) | 1 (Reference) 2.04 (1.25, 3.33)** | 1 (Reference) 1.17 (0.80, 1.69) |
| Colorectal cancer (153–154) | 1 (Reference) 0.92 (0.60, 1.39) | 1 (Reference) 0.78 (0.66, 0.91)** |
| Liver cancer (155) | 1 (Reference) 1.73 (1.32, 2.26)** | 1 (Reference) 1.10 (0.96, 1.27) |

**TABLE 4.** Cox Model With Hazard Ratio and 95% confidence intervals of Cancer Types Associated With Spinal Cord Injury, Stratified by Age

| Variable (ICD-9-CM) | Adjusted HR (95% CI) | Adjusted HR (95% CI) |
|---------------------|----------------------|----------------------|
| All                 | 1 (Reference) 1.24 (1.11, 1.40)** | 1 (Reference) 0.98 (0.93, 1.04) |
| Hematologic malignancy (200–208) | 1 (Reference) 0.87 (0.47, 1.63) | 1 (Reference) 1.41 (1.11, 1.79)** |
| Esophagus cancer (150) | 1 (Reference) 2.04 (1.25, 3.33)** | 1 (Reference) 1.17 (0.80, 1.69) |
| Colorectal cancer (153–154) | 1 (Reference) 0.92 (0.60, 1.39) | 1 (Reference) 0.78 (0.66, 0.91)** |
| Liver cancer (155) | 1 (Reference) 1.73 (1.32, 2.26)** | 1 (Reference) 1.10 (0.96, 1.27) |

**CAD** = coronary artery disease, **CI** = confidence interval, **COPD** = chronic obstructive pulmonary disease, **HR** = hazard ratio, **ICD-9-CM** = International Classification of Diseases Ninth Revision Clinical Modification, **SCI** = spinal cord injury.

**\(P < 0.01.\)**

**\(P < 0.001.\)**

\(^{1}\)Adjusted HR: multivariate analysis, including sex and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.
SCI (≥50 year) had a significantly lower colorectal cancer risk, but this difference was not present among younger patients with SCI. In addition, observational studies and meta-analyses have associated osteoporosis with unchanged or decreased colorectal cancer risk.31–33 Regarding other non-GU cancers, McGlynn et al reported that female patients with osteoporosis had a significantly higher risk of liver cancer and hematologic malignancy compared with female patients without osteoporosis.28 The women with SCI in the current study also exhibited a significantly higher risk of liver cancer and hematologic malignancy than women without SCI. Other research has found inconclusive results for the risk of different non-GU cancers among patients with osteoporosis.29,30

Factors other than SCI-related complications may mediate the possible association between non-GU cancer and SCI. Chronic inflammatory state and immune impairment are also typically observed following SCI.17,45 Substantial evidence suggests that chronic inflammation can play a pivotal role in the initiation, development, and progression of cancers.46–49 Impaired immune response may also contribute to the development and progression of some types of cancer.39–51 The main strength of this study is its use of a nationwide population-based database, which ensures the high generalizability of the findings. The findings may be helpful to our government in considering future policy plan in the field of cancer surveillance. The present results, however, should be interpreted in light of several limitations. First, surveillance bias may have existed. For example, we assumed that the SCI group received less frequent colonoscopy screenings than did the control group, and it can mislead to an underestimated risk of colorectal cancer in SCI group. By contrast, more hematologic malignancies were detected in the patients with SCI, likely because these patients received more blood tests during their more frequent hospital stays. Second, neither patient lifestyle and behavior information (such as tobacco use and alcohol consumption) nor tumor characteristics (such as histology, grade, and stage) were included in the NHIRD; thus, these factors which may affect the results in either direction, could not be adjusted for in this study. Third, patients with SCI are highly prevalent with metabolism disarrangement, malnutrition, and inflammation; however, the NHIRD lacks data of liver function, renal function, inflammation markers, and nutrition markers, so we cannot adjust these factors to eliminate the possible confounding. Fourth, the evidence derived from a cohort study is generally of a lower methodological quality than that obtained from a randomized trial because a cohort study design is subject to several biases related to adjusting for confounding effects. In a retrospective study, lack of baseline data, residual confounding, selection bias, and death competing factor are the major drawbacks. Despite the intrinsic limitations of the NHIRD administrative data, the information that we obtained on the diagnosis of SCI and cancer was highly reliable.

### TABLE 5. Cox Model With Hazard Ratios and 95% Confidence Intervals of Cancer Types Associated With Spinal Cord Injury, Stratified by Follow-up Duration

| Variable (ICD-9-CM) | Follow-up Duration | Adjusted HR† (95% CI) | Follow-up Duration | Adjusted HR† (95% CI) |
|---------------------|--------------------|----------------------|--------------------|----------------------|
|                     | ≤5 Years SCI       |                      | ≥5 Years SCI       |                      |
|                     | No (N = 69,839)    | Yes (N = 19,101)     | No (N = 97,569)    | Yes (N = 22,799)     |
| All                 | 1 (Reference)      | 0.99 (0.93, 1.05)    | 1 (Reference)      | 0.99 (0.90, 1.08)    |
| Hematologic malignancy (200–208) | 1 (Reference) | 1.45 (1.11, 1.89)** | 1 (Reference) | 0.95 (0.63, 1.43) |
| Esophagus cancer (150) | 1 (Reference) | 1.11 (0.75, 1.64) | 1 (Reference) | 1.93 (1.23, 3.03)** |
| Colorectal cancer (153–154) | 1 (Reference) | 0.70 (0.58, 0.84)** | 1 (Reference) | 0.93 (0.73, 1.17) |
| Liver cancer (155) | 1 (Reference) | 1.25 (1.09, 1.44)** | 1 (Reference) | 0.93 (0.73, 1.17) |

CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, SCI = spinal cord injury.

* * * P < 0.01.

† Adjusted HR: multivariate analysis, including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.
In summary, our study suggested that SCI may be related to the risk of specific types of cancer, either increased or decreased risks, and it is not fully consistent with previous reports. The mechanism of this relationship remains undetermined; however, indirect links mediated by some complications of SCI and cancer may account for it. The intricate interaction between cancer and different complications may complicate this association between SCI and non-GU cancers.

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