Medicine®

OBSERVATIONAL STUDY

OPEN

Risk of Nongenitourinary Cancers in Patients With Spinal Cord Injury

A Population-based Cohort Study

Chia-Hong Kao, MD, Li-Min Sun, MD, Yueh-Sheng Chen, PhD, Cheng-Li Lin, MSc, Ji-An Liang, MD, Chia-Hung Kao, MD, and Ming-Wei Weng, MD

Abstract: Little information is available regarding the risk of nongenitourinary (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.

(*Medicine* 95(2):e2462)

Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, GU = Genitourinary, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, LHID 2000 = Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Database, SCI = Spinal cord injury.

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

Editor: Helen Gharaei.
Received: September 21, 2015; revised: December 11, 2015; accepted: December 13, 2015.
From the Lab of Biomaterials, School of Chinese Medicine, China Medical University, Taichung (C-HK, Y-SC), Department of Chinese Medicine, Taipei Medical University Hospital, Taipei (C-HK), Department of Radiation Oncology, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung (L-MS), Department of Bioinformatics and Medical Engineering, Asia University, Wufeng District, Taichung, Taiwan (Y-SC), Management Office for Health Data, China Medical University Hospital (C-LL), College of Medicine, China Medical University (C-LL), Graduate Institute of Clinical Medical Science, School of Medicine, College of Medicine, China Medical University (J-AL, C-HK), Department of Radiation Oncology, China Medical University Hospital (J-AL), Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung (C-HK); and Department of Internal Medicine, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan (M-WW).

Correspondence: Chia-Hung Kao, MD, Graduate Institute of Clinical Medical Science, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 40447, Taiwan (e-mail: d10040@mail.cmuh.org.tw). Ming-Wei Weng, MD, Department of Internal Medicine, Zuoying Branch of Kaohsiung Armed Forces General Hospital, 553 Junxiao Rd, Zuoying District, Kaohsiung, 81345, Taiwan (e-mail: wei630213@yhaoo.com.tw).

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212–113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103–2325-B-039 -006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and Health, and welfare surcharge of tobacco products, China Medical University Hospital Cancer Research Center of Excellence (MOHW104-TDU-B-212–124–002, Taiwan).

Chia-Hong Kao and Li-Min Sun are equally contributory to this manuscript.
Author Contributions: All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript: Conception/Design: Chia-Hong Kao, Li-Min Sun, Chia-Hung Kao; Ming-Wei Weng, Provision of study materials: Chia-Hung Kao; Collection and/or assembly of data: All authors; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors.
The authors have no conflicts of interest to disclose.
Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.
This is an open access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be changed in any way or used commercially.
ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002462

patients with SCI.[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.[12]

Scant information is available regarding the risk of non-GU cancers in patients with SCI. Studies investigating colonoscopic lesions in patients with SCI have reported inconsistent results.[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.[16] Spinal cord injury changes body composition, metabolism, and hormonal regulation over time[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).[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.[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 scrambles 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 140–208) (N = 1037), an age of <20 years (N = 2750), missing information on age or sex (N = 5) were excluded. The remaining 41,900 patients with SCI were considered as the SCI cohort. For each patient with SCI, 4 comparison patients without SCI at the baseline were selected, used same exclusion criteria and frequency-matched by age (per 5 year), sex, year of index date, and comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, and 496), heart failure (ICD-9-CM code 428), coronary artery disease (CAD; ICD-9-CM codes 410–414), and stroke (ICD-9-CM codes 430–438) as the non-SCI cohort.

Outcome

Each subject was monitored from the index date until a new diagnosis 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 χ^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

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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

	Spinal Cord Injury		
Variable	**No N = 167,408**	**Yes N = 41,900**	***P* Value**
Sex	N (%)	N (%)	0.96
Female	61,277 (36.6)	15,343 (36.6)	
Male	106,131 (63.4)	26,557 (63.4)	
Age, mean (SD)	51.8 (18.4)	52.2 (18.2)	0.001*
Stratify age			0.99
≤49	79,210 (47.3)	19,820 (47.3)	
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 (8.31)	0.74
Stroke	12,526 (7.48)	3159 (7.54)	0.69

χ^2 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

	SCI		Control			
Cancer (ICD-9-CM)	**Case**	**Rate#**	**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(200–208)	99	0.42	334	0.33	1.26 (1.01, 1.57)*	1.32 (1.06, 1.65)*
Head and neck (140–149, 161)	196	0.83	754	0.75	1.10 (0.94, 1.29)	1.14 (0.97, 1.33)
Esophagus cancer (150)	59	0.25	181	0.18	1.38 (1.03, 1.86)*	1.45 (1.08, 1.95)*
Stomach cancer (151)	95	0.40	363	0.36	1.11 (0.89, 1.39)	1.19 (0.95, 1.50)
Colorectal cancer (153–154)	208	0.88	1169	1.16	0.76 (0.65, 0.88)***	0.80 (0.69, 0.93)**
Liver cancer (155)	331	1.40	1212	1.21	1.16 (1.03, 1.31)*	1.22 (1.08, 1.38)**
Pancreas cancer (157)	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)
Brain cancer (191)	15	0.06	61	0.06	1.04 (0.59, 1.83)	1.06 (0.61, 1.87)
Thyroid cancer (193)	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.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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

	Men With SCI		Female with SCI	
	No (N = 106,131)	Yes (N = 26,557)	No (N = 61,277)	Yes (N = 15,343)
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.

* $P < 0.05$.

** $P < 0.01$.

† Adjusted HR: multivariate analysis, including age and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.

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 ≥70 years age group.[28] 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. Older patients with

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

	Age ≤ 49 Years SCI		Age ≥ 50 years SCI	
	No (N = 79,210)	Yes (N = 19820)	No (N = 88,198)	Yes (N = 22,080)
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.

** $P < 0.01$.

*** $P < 0.001$.

† Adjusted HR: multivariate analysis, including sex and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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

	Follow-up Duration ≤5 Years SCI		Follow-up Duration >5 Years SCI	
	No (N = 69,839)	Yes (N = 19,101)	No (N = 97,569)	Yes (N = 22,799)
Variable (ICD-9-CM)	Adjusted HR† (95% CI)		Adjusted HR† (95% CI)	
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)	0.89 (0.68, 1.10)
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.

** $P < 0.01$.

*** $P < 0.001$.

† Adjusted HR: multivariate analysis, including age, 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 drugs 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]

Changed body composition and inflammatory activity among patients with SCI may contribute to the higher incidence of metabolic syndrome (obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density lipoprotein levels).[17,19,20,34] Metabolic syndrome is a well-documented risk factor for some cancers.[35–37] Prospective cohort studies have shown associations between metabolic syndrome, and increased risk of breast cancer, colorectal cancer, esophageal adenocarcinoma, and hepatocellular carcinoma.[35,36]Although we matched and adjusted the risk factors of diabetes, hypertension, and hyperlipidemia in this study, these are considered comorbidities rather than complications in the analyses. Our study revealed a significantly higher risk of esophageal and liver cancer among patients with SCI and also concluded that metabolic syndrome after SCI may play a role in this association.

Venous thromboembolism, including deep venous thrombosis and pulmonary embolism, is a well-documented complication during the hospital course of patients with acute SCI.[21,22,38] At least 3 major reasons for this association have been identified: stasis, hypercoagulability, and intimal injury.[39–41] Several large epidemiological studies have reported an increased risk of cancer after diagnosis of idiopathic VTE.[42–44] The VTE factor may partially account for the higher incidence rate of some cancer types among the patients with SCI in our study.

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.[49–51]

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.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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.

REFERENCES

1. Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey? *Spinal Cord.* 2006;44:523–529.
2. Takeshita K, Ando Y, Ohtani K, et al. Incidence of spinal cord injury worldwide: a systematic review. *Neuroepidemiology.* 2010;34:184–192.
3. Donald JW, Sadowsky C. Spinal-cord injury. *Lancet.* 2002;359: 417–425Review.
4. Wu JC, Chen YC, Liu L, et al. Effects of age, gender, and socioeconomic status on the incidence of spinal cord injury: an assessment using the eleven-year comprehensive nationwide database of Taiwan. *J Neurotrauma.* 2012;29:889–897.
5. Strauss DJ, DeVivo MJ, Paculdo DR, et al. Trends in life expectancy after spinal cord injury. *Arch Phys Med Rehabil.* 2006;87:1079–1085.
6. Braithwaite D, Boffetta P, Rebbeck TR, et al. Cancer prevention for global health: a report from the ASPO International Cancer Prevention Interest Group. *Cancer Epidemiol Biomarkers Prev.* 2012;21:1606–1610.
7. Bartoletti R, Gavazzi A, Cai T, et al. Prostate growth and prevalence of prostate diseases in early onset spinal cord injuries. *Eur Urol.* 2009;56:142–148.
8. Patel N, Ngo K, Hastings J, et al. Prevalence of prostate cancer in patients with chronic spinal cord injury. *PM R.* 2011;3:633–636.
9. Shim HB, Jung TY, Lee JK, et al. Prostate activity and prostate cancer in spinal cord injury. *Prostate Cancer Prostatic Dis.* 2006;9:115–120.
10. Groah SL, Weitzenkamp DA, Lammertse DP, et al. Excess risk of bladder cancer in spinal cord injury: evidence for an association between indwelling catheter use and bladder cancer. *Arch Phys Med Rehabil.* 2002;83:346–351.
11. Kalisvaart JF, Katsumi HK, Ronningen LD, et al. Bladder cancer in spinal cord injury patients. *Spinal Cord.* 2010;48:257–261.
12. Lee WY, Sun LM, Lin CL, et al. Risk of prostate and bladder cancers in patients with spinal cord injury: a population-based cohort study. *Urol Oncol.* 2014;32:51e1–517e.
13. Rabadi MH, Vincent AS. Colonoscopic lesions in veterans with spinal cord injury. *J Rehabil Res Dev.* 2012;49:257–263.
14. Han SJ, Kim CM, Lee JE, et al. Colonoscopic lesions in patients with spinal cord injury. *J Spinal Cord Med.* 2009;32:404–407.
15. Stone JM, Nino-Murcia M, Wolfe VA, et al. Chronic gastrointestinal problems in spinal cord injury patients: a prospective analysis. *Am J Gastroenterol.* 1990;85:1114–1119.
16. Frisbie JH, Chopra S, Foo D, et al. Colorectal carcinoma and myelopathy. *J Am Paraplegia Soc.* 1984;7:33–36.
17. Kostovski E, Iversen PO, Hjeltnes N. Complications of chronic spinal cord injury. *Tidsskr Nor Laegeforen.* 2010;130:1242–1245.
18. Tan CO, Battaglino RA, Morse LR. Spinal cord injury and osteoporosis. Causes, mechanisms, and rehabilitation strategies. *Int J Phys Med Rehabil.* 2013;1:pii:127.
19. Kocina P. Body composition of spinal cord injured adults. *Sports Med.* 1997;23:48–60.
20. Bauman WA, Spungen AM. Metabolic changes in persons after spinal cord injury. *Phys Med Rehabil Clin N Am.* 2000;11:109–140.
21. Furlan JC, Fehlings MG. Role of screening tests for deep venous thrombosis in asymptomatic adults with acute spinal cord injury: an evidence-based analysis. *Spine.* 2007;32:1908–1916.
22. Mackiewicz-Milewska M, Jung S, Kroszczyński AC, et al. Deep venous thrombosis in patients with chronic spinal cord injury. *J Spinal Cord Med.* 2015Epub ahead of print.
23. Database National Health Research Institutes (NHRI), Taiwan. http://nhird.nhri.org.tw/en/index.html. Accessed September 10. 2015
24. Morris BP, Kucchal T, Burgess AN. Colonoscopy after spinal cord injury: a case-control study. *Spinal Cord.* 2015;53:32–35.
25. Johnston MV, Diab ME, Chu BC, et al. Preventive services and health behaviors among people with spinal cord injury. *J Spinal Cord Med.* 2005;28:43–54.
26. Lavela SL, Weaver FM, Smith B, et al. Disease prevalence and use of preventive services: comparison of female veterans in general and those with spinal cord injuries and disorders. *J Womens Health (Larchmt).* 2006;15:301–311.
27. Jiang SD, Jiang LS, Dai LY. Mechanisms of osteoporosis in spinal cord injury. *Clin Endocrinol (Oxf).* 2006;65:555–565.
28. McGlynn KA, Gridley G, Mellemkjaer L, et al. Risks of cancer among a cohort of 23,935 men and women with osteoporosis. *Int J Cancer.* 2008;122:1879–1884.
29. Ji J, Sundquist K, Sundquist J. Cancer risk after hospitalization for osteoporosis in Sweden. *Eur J Cancer Prev.* 2012;21:395–399.
30. Cauley JA, Lucas FL, Kuller LH, et al. Bone mineral density and risk of breast cancer in older women: the study of osteoporotic fractures. Study of Osteoporotic Fractures. Research Group. *J Am Med Assoc.* 1996;276:1404–1408.
31. Eiken P, Vestergaard P. Oral bisphosphonates and colon cancer: an update. *Ther Adv Musculoskelet Dis.* 2015;7:160–168.
32. Osteoporosis drug may reduce colon cancer risk. *Mayo Clin Health Lett.* 2011;29:4.
33. Sun LM, Lin MC, Muo CH, et al. Calcitonin nasal spray and increased cancer risk: a population-based nested case-control study. *J Clin Endocrinol Metab.* 2014;99:4259–4264.
34. Yekutiel M, Brooks ME, Ohry A, et al. The prevalence of hypertension, ischaemic heart disease and diabetes in traumatic spinal cord injured patients and amputees. *Paraplegia.* 1989;27:58–62.
35. Doyle SL, Donohoe CL, Lysaght J, et al. Visceral obesity, metabolic syndrome, insulin resistance and cancer. *Proc Nutr Soc.* 2012;71:181–189.
36. Bugianesi E. Review article: steatosis, the metabolic syndrome and cancer. *Aliment Pharmacol Ther.* 2005;22:40–43.
37. Watanabe S, Holo M, Nagahara A. Metabolic syndrome and gastrointestinal disease. *J Gastroenterol.* 2007;42:267–274.
38. Chung SB, Lee SH, Kim ES, et al. Incidence of deep vein thrombosis after spinal cord injury: a prospective study in 37 consecutive patients with traumatic or nontraumatic spinal cord injury treated by mechanical prophylaxis. *J Trauma.* 2011;71:867–870.
39. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation.* 2003;107:16–19.
40. Miranda AR, Hassouna HI. Mechanisms of thrombosis in spinal cord injury. *Hematol Oncol Clin North Am.* 2000;14:401–416.
41. Winemiller MH, Stolp-Smith KA, Silverstein MD, et al. Prevention of venous thromboembolism in patients with spinal cord injury: effects of sequential pneumatic compression and heparin. *J Spinal Cord Med.* 1999;22:182–191.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

42. Sorensen HT, Mellemkjaer L, Steffensen FH, et al. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med.* 1998;338:1169–1173.
43. White RH, Chew HK, Zhou H, et al. Incidence of venous thromboembolism in the year before the diagnosis of cancer in 528,693 adults. *Arch Intern Med.* 2005;165:1782–1787.
44. Nordstrom M, LIndblad B, Anderson H, et al. Deep venous thrombosis and occult malignancy: an epidemiological study. *Br Med J.* 1994;308:891–894.
45. Allison DJ, Ditor DS. Immune dysfunction and chronic inflammation following spinal cord injury. *Spinal Cord.* 2015;53:14–18.
46. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park).* 2002;16:217–226.
47. Chai EZ, Siveen KS, Shanmugam MK, et al. Analysis of the intricate relationship between chronic inflammation and cancer. *Biochem J.* 2015;468:1–15.
48. Sethi G, Shanmugam MK, Ramachandran L, et al. Multifaceted link between cancer and inflammation. *Biosci Rep.* 2012;32: 1–15.
49. Tan TT, Coussens LM. Humoral immunity, inflammation and cancer. *Curr Opin Immunol.* 2007;19:209–216.
50. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol.* 2004;5:617–625.
51. De Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer.* 2006;6:24–37.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.