Risk of Colorectal Cancer in Type 2 Diabetic Patients: A Population-based Cohort Study

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Objective: Most of the existing findings on the association between diabetes mellitus and colorectal cancer were generated from studies in Western societies. However, significant differences in cancer incidence and cancer-prone lifestyles are apparent between Asian and Western countries. This study aims to estimate the risks of colorectal cancer in the diabetic population in Taiwan by conducting a large-scale, controlled cohort study.

Methods: From Taiwan’s Longitudinal Health Insurance Database 2005 (LHID2005), a total of 37 001 diabetic patients were identified. We also obtained data for four controls per patient, matched for sex, age and year of first entry into the LHID2005. All patients were followed up from the date of entry into the LHID2005 until they developed colorectal cancer or to the end of 2006, whichever was earlier. We used Cox’s regression models to assess the risk of developing colorectal cancer, with adjustment for sex, age, comorbid disorders, and socioeconomic characteristics.

Results: We identified 37 001 diabetic patients and 148 004 controls. The adjusted hazard ratio for colorectal cancer in diabetes mellitus patients was 2.1 (95% confidence interval, 1.82–2.42) compared with controls. The risk was significant to both men and women. The adjusted hazard ratios for colorectal cancer were 2.03 (95% confidence interval, 1.68–2.47) in male diabetes mellitus patients and 2.17 (95% confidence interval, 1.77–2.67) in female diabetes mellitus patients.

Conclusions: Our findings based on a large population-based cohort study provide evidence that diabetes mellitus may increase the risk of colorectal cancer in Asians.

Key words: colorectal cancer – DM – risk factors – incidence – epidemiology

INTRODUCTION

Colorectal cancer is one of the most common types of cancer and it causes considerable mortality worldwide (1,2). Several risk factors have been associated with colorectal cancer, including a Western diet, lack of physical activity, smoking and obesity (3–5). Diabetes mellitus (DM), another disease increasing in global prevalence, has shown risk factors similar to those associated with colorectal cancer (6,7). Several studies have suggested a close link between DM and colorectal cancer (8–20). However, the majority of...
these studies were conducted using a case–control design or with a limited number of study subjects (8–13). Moreover, some population-based cohort studies have been limited to either male or female diabetic patients (12,13). A recent meta-analysis on 41 studies associated DM with an increased incidence of colorectal cancer [relative risk, 1.27; 95% confidence interval (CI), 1.21–1.34] (20).

Most of the existing findings on the association between DM and colorectal cancer were generated from studies in Western societies (8–13). However, significant differences in cancer incidence and cancer-prone lifestyles are apparent between Asian and Western countries (15). The positive association between DM and colorectal cancer with regard to sex and different ethnic population has proved inconclusive thus far. For example, no associations between DM and colon cancer were evident among African Americans (21). A large-scale, population-based study in Japan suggested that diabetic men carried a higher risk for colorectal cancer than diabetic women did (16). Studies from other Asian countries also have yielded inconsistent results related to sex-related prevalence in the association between DM and colon cancer (17–19). Thus, taking advantage of Taiwan’s nationwide, population-based database, we conducted a large-scale, controlled cohort study to estimate the hazard rates and relative risks of colorectal cancer in the diabetic population.

METHODS

DATA SOURCE

We obtained data from the Taiwan’s Longitudinal Health Insurance Database 2005 (LHID2005), which is part of the Taiwan National Health Insurance Research Database (NHIRD). In March 1995, the National Health Insurance (NIH) program was initiated in Taiwan as a means of financing health care for all citizens of Taiwan. According to the Ministry of Interior, over 22 million are currently enrolled, covering >98% of the entire population of Taiwan (22). The LHID2005 contains the entire claim file for each of 1 000 000 beneficiaries who were sampled randomly from the NHIRD in 2005. The data in each file include ambulatory care; inpatient care; pharmacy use; dates of service; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes and medical expense claims (23). The available reimbursement databases extended back to 1996. Since our study used anonymous secondary data from the LHID2005, it was exempt from full review by an independent review board.

STUDY DESIGN AND STUDY POPULATION

We identified the DM study cohort from ICD-9-CM codes 250.1 to 250.9, and the colorectal cancer cohort from ICD-9-CM codes 153 to 154. Our study cohorts comprised subjects aged 18 years and over who had been identified as having experienced at least two consistent ICD-9-CM diagnoses of DM between 1 January 2004 and 31 December 2005. We excluded patients who were diagnosed with type 1 DM, who had only one record of DM during this time frame, who lacked an identification number or date of birth and who were diagnosed with colon cancer before they were diagnosed with DM. In the most conditions, those who had only one record of DM were not valid DM patients. Subjects came on the suspicion of having DM, so their blood sugar or HBA1c was checked. If the blood sugar or HBA1c was normal, DM was no more in the diagnosis. In that condition, the patient will have only one record for DM.

We created the control group from the patients who remained in the LHID2005; we excluded patients with any record of DM from 1 January 2004 to 31 December 2005, and those who lacked an identification number or date of birth. We matched four controls to each DM patient according to age (18–30, 31–40, 41–50, 51–60 and >70 years), sex and the year of entry into the LHID2005. We did not use the entire cohort from LHID2005 because we have to match the time frame of entry into the insurance between the DM patients and the control group. The final cohorts included 37,001 DM patients and 148,004 control patients. All subjects were followed up until they developed colorectal cancer or until up to 3 years from the day of entry, whichever was earlier.

BASELINE VARIABLES

For DM patients and control patients, the baseline variables, including age, sex, level of urbanization, cardiovascular disease (CVD), chronic liver disease, nephropathy and autoimmune disease, were obtained from the LHID2005. We divided the comorbid medical disorders according to ICD-9-CM codes into the following categories: CVD [stroke (ICD-9-CM codes, 430–438), hypertension (401–405), ischemic heart disease (410–414) and peripheral arterial disease (250.7, 785.4, 443.81 and 440–448)]; chronic liver disease [hepatitis B (070.2, 070.3 and V02.61), hepatitis C (070.41, 070.44, 070.51, 070.54 and V02.62), unspecified chronic hepatitis (070.9, 571.4, 571.8 and 571.9), alcoholic liver disease (571.0, 571.1, 571.2 and 571.3), cirrhosis (571.5 and 571.6) and biliary tract disease (574–576)]; nephropathy (580–589) and autoimmune disease (710.0, 710.1, 714.0, 710.4, 710.3, 446.0, 446.2, 446.4, 446.5, 443.1, 446.7, 446.1, 136.1, 694.4, 710.2, 555 and 556).

STATISTICAL ANALYSIS

Pearson’s χ² tests and Fisher’s exact test were used to compare the data points in Table 1. The CIs for incidence rates were evaluated based on a common application of Poisson CIs (Table 2).

To assess the risk of developing colorectal cancer within 3 years of a DM diagnosis, we conducted a multivariate survival analysis using Cox regression models to examine the
hazard ratio (HR) of the two cohorts for colorectal cancer after adjusting for confounding factors such as patient age, sex, level of urbanization, CVD, chronic liver disease, nephropathy and autoimmune disease. As to the urbanization level, all 359 cities/towns in Taiwan are stratified into 7 levels according to standards published by the Taiwanese NHRI, with 1 referring to ‘most urbanized’ and 7 referring to ‘least urbanized’. For our study, levels 1 and 2 were combined into a single group, referred to as urban; levels 3 and 4 were combined into a single group, referred to as suburban and the remaining three levels (5, 6 and 7) were combined into a single group, thereafter referred to as rural. To satisfy the proportional hazards assumption, we investigated diagnostic log–log survival plots for each dichotomous variable in the model.

We conducted a sensitivity analysis by using the bootstrap approach, which is a robust method of validating Cox regression models (24,25). Patients were required to have at least 6 months of follow-up without developing colorectal cancer. To avoid errors associated with too many variables, we minimized interference error by using the propensity score as a variable (26). The propensity score was predicted on the basis of logistic regression from confounding factors, which included age, sex, CVD, chronic liver disease, nephropathy, autoimmune disease and level of urbanization. The bootstrap HR corresponded to the median HR that was observed among 1000 replications; the 95% CI was derived from the 2.5 and 97.5 percentiles of the bootstrap distribution.

All data analyses were performed using the SAS statistical package (ver. 9.1.3; SAS Institute, Cary, NC, USA). A two-tailed \( P < 0.05 \) was used to determine significance.

### RESULTS

We identified 37 001 DM patients and 148 004 age- and sex-matched controls (Fig. 1). Baseline characteristics and comorbid medical disorders are listed in Table 1. Compared with the controls, DM patients displayed higher rates of CVD, chronic liver disease, nephropathy and autoimmune disease (all \( P < 0.001 \)).

Cox regression analysis showed that the incidence of colorectal cancer was significantly higher in DM patients than in control patients (HR, 2.10; 95% CI, 1.82–2.42; Table 2). All
covariates (confounding factors including age, sex, CVD, chronic liver disease, nephropathy, autoimmune disease and level of urbanization) were balanced within the DM and control groups and adjusted for propensity score. The incidence of colorectal cancer remained significantly higher in DM patients than in control patients (HR, 2.07; 95% CI, 1.78–2.36; Table 2). The sensitivity analyses for the Cox model confirmed the risk of colorectal cancer in DM patients when they were assessed for the development of colorectal cancer within 6 months (Table 2).

Additionally, we analyzed the data that were stratified by patient sex (Table 3). The incidence of colorectal cancer is higher in males than in females (adjusted HR, 1.34; 95% CI, 1.18–1.53). The adjusted HR for colorectal cancer in male DM patients was 2.03 (95% CI, 1.68–2.47). A similar result was observed in female DM patients. The adjusted HR for the occurrence of colorectal cancer in female DM patients was 2.17 (95%, CI 1.77–2.67), which was higher than the HR in the comparison cohort.

DISCUSSION

Our study demonstrates a significant positive association between DM and incident colorectal cancer, illustrated by an ~2-fold increase in risk compared with age- and sex-matched control subjects after adjusting for various clinical risk factors. The risk was significant to both men and women.

Our study population comprised patients of Asian ethnicity, whereas previous studies comprised primarily non-Asian patients. The relationship between DM and
colorectal cancer has been explored in a number of different Asian studies (16–19). In contrast to most studies on Western populations, the studies on Asian populations have not provided consistent results regarding the relationship between DM and the risk of colorectal cancer. The study conducted by Jee et al. in Korea showed a significantly higher risk found in overall diabetic patients (including women and men) (HR, 1.13; 95% CI, 1.03–1.23), but the risk did not increase separately when dividing into each diabetic men (HR, 1.11; 95% CI, 1.00–1.24) and women (HR, 1.17; 95% CI, 0.98–1.40) (18). Similar results have also been obtained from studies in Japan (16,19), but a study on cancer registries performed in Chinese populations of Singapore revealed a significant association between DM and the risk of colon cancer in diabetic men (HR, 1.5; 95% CI, 1.2–2.1) and in diabetic women (HR, 1.4; 95% CI, 1.0–1.9) (18). However, the DM diagnosis in these studies was based on data generated from a self-report questionnaire, and thus, the results should be interpreted with caution. Regarding the impact of DM on colorectal cancer, our findings are consistent with most of the relevant literature (8–14).

Our study has several strengths. First, in contrast to the groups used in previous Asian studies (16–19), our diabetic and control groups were retrieved from the Taiwan NHIRD, which is a population-based and highly representative database, allowing little possibility for recall and selection bias. Secondly, we identified carcinoma in our study by valid and definite means. In the NHIRD, biopsy and histological verifications are required before carcinoma can be diagnosed definitively and the treatment can be initiated. In the NHI program of Taiwan, the subjects with malignancy will have ‘catastrophic illness card’ and who is exempted from paying copayments. The diagnosis and quality of cancer information in LHID is confirmed based on the NHI Catastrophic Illness card. We were able to use insurance claim data sets within a clinical research setting by accessing longitudinal records from a large sample of patients from various geographic regions. By using medical records, we also reduced potential bias related to self-reporting. In addition, the likelihood of non-response and follow-up loss of cohort member was decreased. Therefore, our study stands alone in its capacity to draw upon an extensive, nationwide, population-based database and it carries the potential for generalization to the population as a whole and to populations similar to Taiwan.

Several mechanisms have been proposed to explain the potential relationship between DM and colorectal cancer. Hyperinsulinemia, insulin-like growth factor-1, glucagon-like peptide-1 and the relative binding proteins each play an important role in metabolism, cell growth, proliferation and the regulation of the apoptotic process in colon cells (27–29). Risk factors such as obesity, physical inactivity, smoking, Western diet and metabolic syndrome are common in both DM and colorectal cancer patients (4).

The NHIRD lacks detailed clinical information, and therefore, we were unable to control for other important confounding factors. It is well known that smoking, obesity, physical inactivity and dietary habits are closely associated with several chronic illnesses such as CVD, nephropathy and liver disease (30–33). Thus, we used propensity score methods to minimize the bias in our analysis between patients with colorectal cancer with or without co-occurring DM. Smoking also is an important confounding factor. However, we were unable to evaluate the effects of smoking directly because NHIRD did not collect this information. We obtained data from the Taiwan National Health Interview Survey 2005 database, which included a random selection of ~20,000 subjects from Taiwan. The entire data set has been released for public use and can be accessed at http://nhis.nhri.org.tw. By taking these steps, we were able to investigate the characteristic differences between diabetic and non-diabetic members of the Taiwanese population. After all the outlined exclusions were made, a total of 14,585 subjects were studied. The prevalence of smoking was 25.9% in patients with diabetes (215 of 829) and 26.6% in patients without diabetes (3655 of 13,756) (P = 0.687). The smoking status is similar between patients with and without DM in Taiwan.

### Table 3. Incidence, crude and adjusted hazard ratios, and 95% confidence intervals for patients stratified by sex

<table>
<thead>
<tr>
<th>Presence of colorectal cancer</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>DM patients</td>
</tr>
<tr>
<td>Follow-up period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>331</td>
<td>166</td>
</tr>
<tr>
<td>Person-years</td>
<td>193,995.87</td>
<td>46,548.81</td>
</tr>
<tr>
<td>Incidence, per 100,000 person-years (95% CI)</td>
<td>170.6 (153.2–190.0)</td>
<td>356.6 (306.4–415.2)</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>1.00</td>
<td>2.12 (1.76–2.55)</td>
</tr>
<tr>
<td>Adjusted HR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>1.00</td>
<td>2.03 (1.68–2.47)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjustments were made for age, CVD, chronic liver disease, nephropathy, autoimmune disease and level of urbanization level.
Several notable limitations were identified in our study. First, we were unable to identify the duration of DM. Secondly, screening or surveillance bias may have occurred; diabetic patients visit physicians more frequently. However, it is difficult to assess whether the significant associations between DM and colorectal cancer were due to frequent disease surveillance among diabetes patients. Thirdly, the NHIRD lacks detailed clinical information, and thus, we were unable to control for other important confounding factors such as BMI, physical inactivity and dietary habit. Finally, colorectal cancer was likely underestimated due to the short follow-up duration.

In conclusion, the sensitivity analyses indicated that the risk of colorectal cancer in patients with DM is fairly robust after excluding incident colorectal cancer within the first 6 months. In conclusion, our findings based on a large population-based cohort study provide evidence that DM may increase the risk of colorectal cancer in Asians.

Conflict of interest statement

None declared.

References