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Type 2 diabetes and the risk of colorectal polyps

A retrospective nationwide population-based study

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Abstract

The incidence rates of type 2 diabetes mellitus (T2DM) and colorectal polyps have been increasing over the last decades. However, direct associations between T2DM and colorectal polyps have not been extensively reported. We will explore the relationship between T2DM and colorectal polyps.

In the retrospective study, we classified DM and NonDM groups (control) from 993,516 people in Taiwan nationwide population insurance database from the period of 2000 to 2013. We collected data on income and comorbidities through the international classification of diseases, ninth revision—clinical modification (ICD-9-CM) codes.

The T2DM group had a higher incidence rate of colorectal polyps (31.97%, 95% confidence interval [CI] = 30.97–33.28) than the control group (25.9%, 95% CI = 25.1–26.72), and the crude incidence ratio was 1.235 (95% CI = 1.174–1.300). In 13 years of follow-up (2000–2013), T2DM was linked to a significantly higher cumulative probability of colorectal polyps (log-rank test: $P = .0001$).

Patients with T2DM had a 1.23-fold higher risk of new colorectal polyps than control patients in 13 years of follow-up. We explain the T2DM increases incidence for colorectal polyps in long term follow-up.

Abbreviations: ICD-9-CM = international classification of diseases, ninth revision—clinical modification, T2DM = type 2 diabetes mellitus.

Keywords: colorectal cancer, colorectal polyps, nationwide population study, type 2 diabetes mellitus

1. Introduction

Colorectal cancer (CRC) is among the leading causes of mortality and morbidity throughout the world, thus representing a major public health problem. It is the third most common cancer worldwide (following tumors of the lungs and breasts) and the fourth most common cause of oncological death.[1] The lifetime risk of colorectal cancer (CRC) in Western countries is approximately 5%. CRC commonly develops from precursor lesions termed polyps.[2] Thus, colorectal polyp screening, detection, and eradication are important for preventing CRC.[3] The removal of polyps in normal daily practice is associated with a low incidence of developing CRC.[4]

Meanwhile, the global prevalence of diabetes mellitus (DM) is increasing.[5] According to the World Health Organization, 422 million people had DM in 2014, and its prevalence grew from 4.7% in 1980 to 8.5% in 2014.[6] In addition, whereas at least 171 million people worldwide had diabetes in 2000, it is estimated that this patient population will almost double by the year 2030.[7] Type 2 DM (T2DM) is also highly correlated with metabolic syndrome, and some studies have reported an association between metabolic syndrome and the risk of colorectal polyps.[8–10] However, direct associations between T2DM and colorectal polyps have not been extensively reported, and long-term data from studies with large populations of different ethnic groups are required to support this relationship.[11]

In this study, we explored the association of T2DM with colorectal polyps through a retrospective cohort study using 13 years of nationwide population data.

2. Materials and methods

2.1. Data source

The Taiwan National Healthcare Insurance Program covers more than 99% of the Taiwanese national population of 23 million and has been continually updated since 1995. The National Health Insurance Research Database (NHIRD) established by the National Health Research Institute of Taiwan Officials is one of the largest and most complete medical

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The present study was conducted in compliance with the declaration of Helsinki and was approved by the institutional review board of Changhua Christian Hospital (CCH IRB No. 191101). Retrospective studies conducted in Taiwan do not require the informed consent of the participants.

The authors have no conflict of interest.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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databases in the world, and it has been used to thoroughly study T2DM. In the database, all information is encrypted to protect the anonymity of the patients. This study met the confidentiality regulations of the international classification of diseases, ninth revision—clinical modification (ICD-9-CM) is a coding scheme for medical insurance reimbursement. The implementation of this research project was consistent with the declaration of Helsinki and was approved by the institutional review board of Changhua Christian hospital (CCH IRB No. 191101). The requirement for participants' informed consent was waived due to it being a retrospective research project.

2.2. Definition of newly identified T2DM

Using the NHIRD, we identified patients older than 18 years of age with T2DM as indicated by ICD-9-CM code 250 in the medical records (Supplementary Table 1, http://links.lww.com/MD/G70). Eligible patients had at least 2 records of outpatient visits within 1 year or 1 admission since 2000. Patients with a DM diagnosis before 2000 were excluded from the study.

2.3. Definition of new colorectal polyps

New colorectal polyps were indicated by ICD-9-CM codes 211.3, 211.4, 153, 154 and from the period of 2000 to 2013 (Supplementary Table 1, http://links.lww.com/MD/G70). Eligible patients had at least 2 medical records of outpatient visits within 1 year or 1 admission, and those diagnosed with polyps prior to 2000 were excluded.

2.4. Inclusion criteria

1. T2DM with ICD-9 code 250 from 2000 to 2013 and older than 18 years of age.
2. The remaining patients with non-type 2 diabetes after screening for exclusion criteria and age-sex match are the control group.

2.5. Exclusion criteria

1. T2DM diagnosis before 2000.
2. Type 1 diabetes mellitus.
3. Diagnosis of colorectal polyps before 2000.
4. Diagnosis of colon cancer before 2000.
5. Unable to match or missing data.

2.6. Statistical analysis

Differences between the T2DM and control groups were evaluated using Student *t* test. The cumulative probability of colorectal polyps was compared between the groups using the Kaplan–Meier method. Comparisons between groups were performed using the log-rank test. The association of risk factors was evaluated using Cox proportional hazards regression modeling. Variables including age, gender, income, and comorbidities were included in the multivariable analysis. All statistical analyses were performed using the SAS version 9.4 statistical program for Windows (SAS Institute Inc., Cary, NC, USA). All tests were two-tailed and a *P* value of less than .05 was considered to indicate a statistically significant difference.

3. Results

A medical database consisting of 993,516 patients treated between 1997 and 2013 was analyzed. We excluded patients as follows: T2DM diagnosis before 2000 (index date), 33,936 patients; diagnosis of type 1 DM, 3111 patients; diagnosis of colorectal polyps before the index date, 1414 patients; diagnosis of colon cancer before the index date, 867 patients; and unable to match or missing data, 871 patients. We then matched patients with T2DM and controls by age and sex at a ratio of 1:2. In total, the study included 92,157 patients who were newly diagnosed with T2DM between 2000 and 2013 and a group of 184,314 patients without T2DM as the control group (Fig. 1).

In terms of basic characteristics, no statistically significant differences were identified between the groups regarding gender, age, and income. Conversely, the T2DM group had higher rates of comorbidities such as hypertension, hyperlipidemia, ischemic heart disease, stroke, chronic obstructive pulmonary disease (COPD). Rheumatoid disease, chronic kidney disease, and chronic liver disease (all $P < .001$, Table 1).

We analyzed the incidence rate of colorectal polyps. The T2DM group had a higher incidence rate of colorectal polyps than the control group (31.97% [95% confidence interval [CI]] = 30.97–33.28 vs 25.9% [95% CI = 25.1–26.72]), and the crude incidence ratio was 1.235 (95% CI = 1.174–1.300) (Table 2). In 13 years of follow-up, T2DM was linked to a significantly higher cumulative probability of colorectal polyps (log-rank test: $P = .0001$) (Fig. 2).

Multivariate analyses using Cox proportional hazard model revealed no significant difference in the risk of colorectal polyps between the T2DM and control groups (hazard ratio [HR] = 1.04, 95% CI = 0.98–1.10, $P = .159$) (Table 3). Meanwhile, male sex (HR = 1.61, 95% CI = 1.51–1.71, $P < .001$) and age ($P < .001$) were significantly associated with colorectal polyp risk. In addition, hypertension (HR = 1.11, 95% CI = 1.04–1.19, $P = .0016$), hyperlipidemia (HR = 1.29, 95% CI = 1.20–1.39, $P < .001$), ischemic heart disease (HR = 1.16, 95% CI = 1.07–1.26, $P = .0001$), COPD (HR = 1.349, 95% CI = 1.255–1.451,

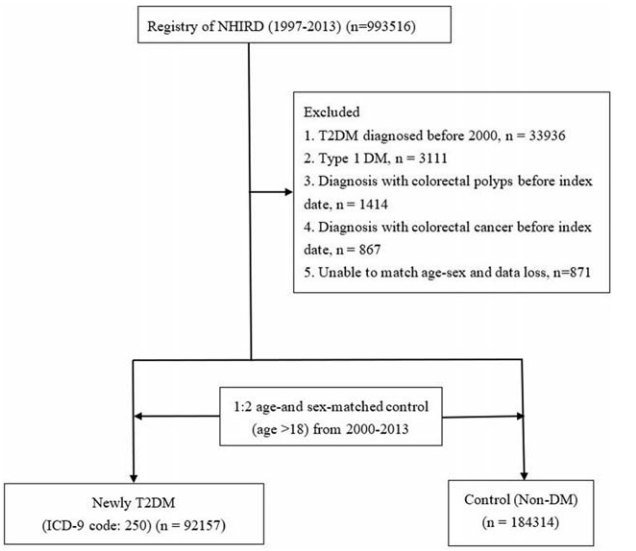

Figure 1. Flow of patients through the study. DM = diabetes mellitus, ICD-9 = international classification of diseases, ninth revision, NHIRD = national health insurance research database, T2DM = type 2 diabetes mellitus.

Table 1

Baseline characteristics among study groups.

	Control n = 184314	Type 2 DM n = 92157	*P* value
Sex			1.0000
Female	87610 (47.53%)	43805 (47.53%)	
Male	96704 (52.47%)	48352 (52.47%)	
Age			1.0000
<30	6278 (3.41%)	3139 (3.41%)	
30-45	30664 (16.64%)	15332 (16.64%)	
45-65	94300 (51.16%)	47150 (51.16%)	
>=65	53072 (28.79%)	26536 (28.79%)	
Low income	1009 (0.55%)	628 (0.68%)	.096
Co-morbidity			
Hypertension	43332 (23.51%)	38628 (41.92%)	<.0001
Hyperlipidemia	19922 (10.81%)	19944 (21.64%)	<.0001
Ischemic heart disease	16878 (9.16%)	14034 (15.23%)	<.0001
Stroke	10382 (5.63%)	8401 (9.12%)	<.0001
COPD	14924 (8.10%)	10727 (11.64%)	<.0001
Rheumatoid disease	3894 (2.11%)	2415 (2.62%)	<.0001
Chronic kidney disease	2243 (1.22%)	1674 (1.82%)	<.0001
Chronic liver diseases	18161 (9.85%)	17033 (18.48%)	<.0001

Values are numbers (%).
COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus.

$P < .001$), chronic kidney disease (HR = 1.341, 95% CI = 1.121–1.604, $P < .001$), and chronic liver disease (HR = 1.373, 95% CI = 1.286–1.466, $P < .001$) were associated with a higher risk of colorectal polyps.

4. Discussion

To the best of our knowledge, this is the first nationwide population base study of the potential relationship between T2DM and colorectal polyps. We report the novel observation of an increased probability of colorectal polyps associated with T2DM.

T2DM increases the risk of CRC,[12] and it is a prognostic factor for this malignancy.[13] A prospective study reported an association between CRC and T2DM in men.[14] Findings from a large Swedish study indicated that the presence of any type of polyp in the colon increases the risk of CRC.[15] This means in addition to hyperplastic or adenomatous polyps, other types of colorectal polyps have malignant potential and the ability to cause CRC. A recent meta-analysis demonstrated that patients with T2DM have a 30% higher risk for CRC than the general population and that this risk is doubled in patients with diabetes who are receiving insulin.[16] The increased risk is related to the duration of insulin therapy, possibly due to increased insulin levels.[17] It has been hypothesized that a high homocysteine level

Table 2

Incidence of colorectal polyps in study group.

	Control n = 184314	Type 2 DM n = 92157
Follow up person months	15165629	7413801
New case	3928	2370
Incidence rate* (95% CI)	25.90 (25.1–26.72)	31.97 (30.71–33.28)
Crude Incidence ratio (95% CI)	Reference	1.235 (1.174–1.300)

*Incidence rate, per 100000 person months.
CI = confidence interval, DM = diabetes mellitus.

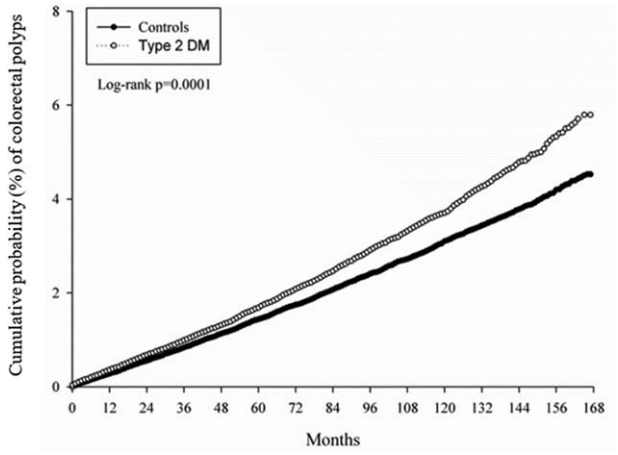

Figure 2. Cumulative probability of colorectal polyps.

is a risk factor for DM.[18,19] In addition, hyperhomocysteinemia plays an important role as a coenzyme in metabolism, which is believed to have a critical role in the progression of colorectal polyps.[20,21,22] Some studies observed an association of hyperhomocysteinemia with aberrant DNA methylation, which may result in the inactivation of tumor suppressor genes and CRC growth.[23,24,25] In our study, we proposed a hypothesis in which T2DM, hyperhomocysteinemia, colorectal polyps, and CRC exert direct or indirect influences on each other.

In our study, the risk of colorectal polyps increased with increasing time since a diagnosis of T2DM. However, this association did not persist in multivariate analysis. We hypothesized that the follow-up time may not have been sufficient to observe an association. A longer duration since the diagnosis of T2DM may provide a longer period for the development of colorectal polyps. On the other hand, polyps correlate with age

Table 3

Multiple Cox proportional hazard regression for estimation of adjusted hazard ratios on colorectal polyps.

Variable	Colorectal polyps aHR (95% CI)	*P* value
Type 2 DM (ref: control)	1.04 (0.98–1.10)	.159
Sex		
Female	1	
Male	1.61 (1.51–1.71)	<.001
Age		
<30	0.27 (0.17–0.43)	<.001
30-45	1	
45–65	2.14 (1.91–2.39)	<.001
≥65	2.31 (2.05–2.61)	<.001
Co-morbidity		
Hypertension	1.11 (1.04–1.19)	.0016
Hyperlipidemia	1.29 (1.20–1.39)	<.001
Ischemic heart disease	1.16 (1.07–1.26)	.0001
Stroke	1.101 (1.004–1.208)	.1446
COPD	1.349 (1.255–1.451)	<.001
Rheumatoid disease	1.114 (0.959–1.293)	.3117
Chronic kidney disease	1.341 (1.121–1.604)	<.001
Chronic liver diseases	1.373 (1.286–1.466)	<.001

aHR = adjusted hazard ratio, CI = confidence interval, ref = reference.

>45 years, male sex, and the presence of hyertension, hyperlipidemia, ischemic heart disease, COPD, chronic kidney and liver disease in multivariate analysis, which implies that it is not type 2 diabetes but rather different chronic diseases which are often associated to type 2 diabetes, which appear to be associated to the development of colorectal polyp risk.

The colorectal cancer screening guideline of the American Gastrointestinal Association recommends that colorectal screening should start at 50 years of age in average-risk persons, and discontinuation of screening should be considered when people who have prior negative screening (particularly colonoscopy) reach 75 years of age or have a life expectation <10 years.[26] Meanwhile, CRC screening starting at 45 years of age is likely to be more cost-effective for average-risk persons.[27] Our findings suggest that among patients with T2DM, males and those with histories of hypertension, hyperlipidemia, ischemic heart disease, and chronic kidney disease should be especially targeted by CRC screening programs.

Regarding comorbidity, we reported that hypertension, hyperlipidemia, ischemic heart disease, COPD, Chronic kidney disease, and chronic liver disease increased the risk of colorectal polyps by 11, 29, 16, 34, 34, and 37% respectively, indicating that other risk factors are involved.

Our study had several strengths, including its nationwide population-based design, large sample size, and long-term and complete follow-up. However, its limitations included the lack of consideration of some confounding factors as well as other factors such as self-paid medication, coding errors in ICD-9-CM medical records, and colorectal polyps that were documented by coding systems rather than pathologically confirmed.

5. Conclusion

Patients with T2DM had a 1.23-fold higher incidence rate of new colorectal polyps than control patients in 13 years of follow-up. In long-term follow-up, patients with T2DM and coincident hypertension, hyperlipidemia, and ischemic heart disease may require more aggressive screening for colorectal polyps to prevent CRC.

Author contributions

Conceptualization: Wei-Wen Su.
Project administration: James Cheng-Chung Wei.
Software: Jing-Yang Huang.
Writing – original draft: Po-Ke Hsu.

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