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CLINICAL STUDY

Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan

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Abstract

Objective: A retrospective cohort study, using a population-based reimbursement database, was conducted for investigating the relationship between diabetes and colon cancer and assessing whether metformin had a protective effect.

Methods: Overall, 493 704 men and 502 139 women, covered by the National Health Insurance, without colon cancer were followed from 2003 to 2005. Cox regression evaluated the adjusted relative risk (RR), considering confounders and detection examinations.

Results: Even though diabetes patients had a significantly higher probability of receiving examinations that could lead to the detection of colon cancer, they had a significantly higher risk (24%) of this cancer after adjustment. Metformin users had a significantly lower risk (27%) of colon cancer. While comparing patients with diabetes for <1, 1–3, and ≥ 3 years to nondiabetes individuals, the adjusted RR (95% confidence interval) was 1.308 (1.020–1.679), 1.087 (0.900–1.313), and 1.185 (1.055–1.330) respectively. The higher risk among those with diabetes for <1 year suggested a possible reverse causality or a link with prediabetes. However, diabetes still might play some role in the development of colon cancer in those with diabetes for ≥ 3 years. The duration of metformin use showed an inverse trend, with a significant RR of 0.643 (0.490–0.845) in users for ≥ 3 years, when compared with nonusers. In addition, metformin may reduce colon cancer risk associated with chronic obstructive pulmonary disease (a surrogate for smoking).

Conclusions: Following adjustment for potential detection bias and other covariates, diabetes remains a significant risk factor for colon cancer. Metformin may protect against colon cancer.

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Introduction

Colon cancer is one of the leading causes of cancer-related deaths in America (1), Europe (2), and Asia (3). Its incidence has been increasing rapidly in recent decades, and it is currently the second most common cause of cancer-related deaths in Taiwan (4). The abrupt increase in the incidence of colon cancer is probably related to factors such as obesity, a sedentary lifestyle, and the consumption of a Western diet with high fat and low fiber, all of which accompanied Taiwan's rapid economic growth (5).

Type 2 diabetes mellitus (T2DM) increases the risk for several types of cancers involving the liver, pancreas, colon, endometrium, bladder, and breast (6, 7, 8, 9, 10, 11). Insulin resistance, hyperinsulinemia, oxidative stress, and proinflammation have been suggested as the potential mechanisms (7, 8). Recent studies have suggested that different antidiabetic therapies may affect the diabetes patients' risk of developing cancer. Among them, insulin (12) and insulin secretagogues (13, 14) may increase this risk, but metformin (15, 16, 17, 18, 19) and possibly thiazolidinedione (20) may reduce it.

Studies on the link between metformin and colon cancer are still sparse and the results are controversial. A recent systematic review and meta-analysis suggested that metformin was associated with a significant overall cancer risk reduction of 31% (21). However, its protective effect could only be demonstrated for pancreatic cancer and hepatocellular carcinoma, and the results were not significant for cancers involving the colon, breast, and prostate (21). In this meta-analysis, only three papers evaluated the effect of metformin on colon cancer risk specifically (12, 16, 17) and the summary relative risk (RR; 95% confidence interval) was 0.64 (0.38–1.08) (21). Another meta-analysis (19), which included a paper from Taiwan (15), estimated a significant summary RR of 0.63 (0.47–0.84). On the other hand, a recent short-term clinical trial evaluating the effect of metformin 250 mg/day ($n=12$) vs no treatment ($n=14$) in nondiabetic patients with rectal aberrant crypt foci (an endoscopic surrogate marker for

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colorectal cancer) for only 1 month found a significantly reduced number of aberrant crypt foci in metformin-treated patients (22). This study strongly indicated a potential inhibitory effect of metformin on colorectal carcinogenesis. Currently, more than ten ongoing clinical trials are aimed at investigating the anticancer effects of metformin on various human malignancies involving the breast, prostate, pancreas, endometrium, kidney, lung, lymphoma, and others (23, 24).

A recent study conducted in the USA showed that diabetes patients, particularly in the first year of diagnosis, are more likely to receive endoscopic examinations of the lower gastrointestinal tract (25). This increases the likelihood that studies evaluating the link between diabetes and colon cancer, without considering the greater frequency of these clinical examinations in diabetes patients, might result in a biased overestimation of the incidence of colon cancer, especially among those with new-onset diabetes. Furthermore, it has not yet been fully evaluated whether the duration of metformin use is an important determinant in its association with colon cancer. Therefore, using the reimbursement databases of the National Health Insurance (NHI) of Taiwan, this study aimed to investigate: i) whether the link between T2DM and colon cancer is independent of detection bias; and ii) whether metformin and the duration of its use are associated with a protective effect against colon cancer.

Materials and methods

Study population

This is a population-based retrospective cohort study. According to the Ministry of Interior, Taiwan, in 2005, >98.0% of the Taiwanese population was covered by the NHI, a single-payer health insurance program launched on March 1, 1995. Each year, the Bureau of NHI collects data, including registration files and original claims data for reimbursement, and sends it to the National Health Research Institutes, as these are the only institutes approved for managing academic research databases. Then, the data files are de-identified by scrambling the identification codes of the patients and medical facilities for the protection of privacy. From January 1, 2005 to January 1, 2006, there were ~25.68 million beneficiaries in the NHI program according to the Registry for Beneficiaries data files. The National Health Research Institutes randomly sampled 1 000 000 beneficiaries from this registry file who were representative of the entire population and created the Longitudinal Health Insurance Database 2005 (LHID 2005). The reimbursement data files of these sampled individuals were compiled for use in academic research (26). The LHID 2005 was approved for use in this study, and the database contained all the longitudinal reimbursement information for the random sample from 1996 to the end of 2005. Information on sex, date of birth, medications, and diagnostic codes of all subjects based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), were retrieved for analyses. Diabetes was coded 250.1–250.9 and colon cancer 153.

As colon cancer is rare in young people, we analyzed the data for all ages and for those aged ≥40 years. Figure 1 shows a flowchart of the selection procedure used in this study. After exclusion of individuals with type 1 diabetes (in Taiwan, patients with type 1 diabetes were issued a 'Severe Morbidity Card' after certified diagnosis), individuals whose region of residence was unknown, and individuals diagnosed with

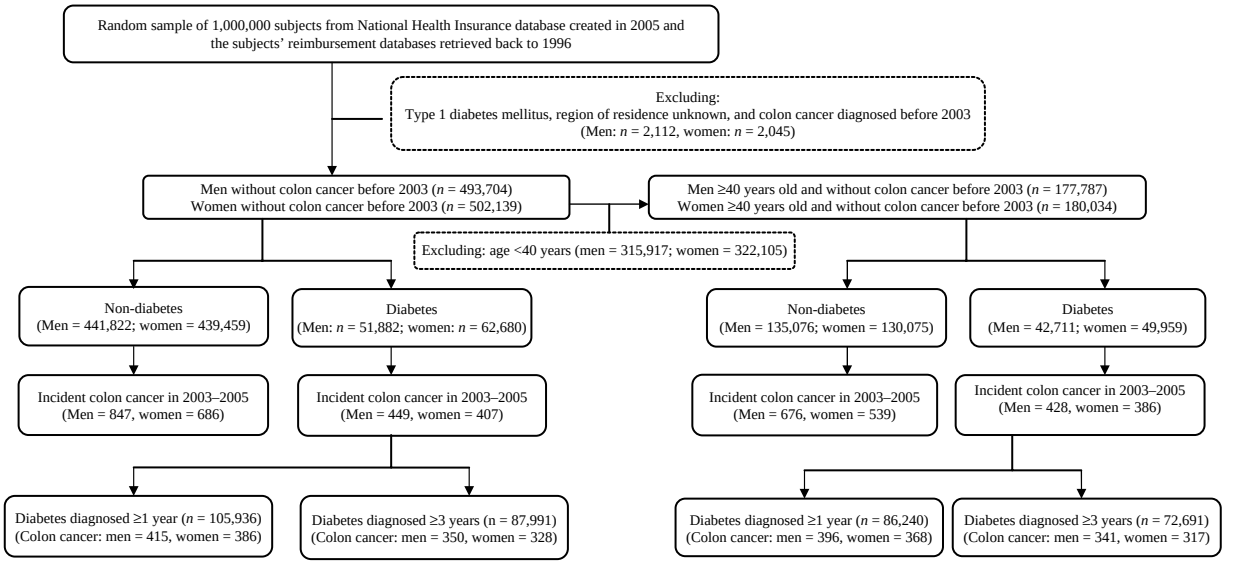

Figure 1 Flowchart showing the selection procedure of study subjects.

colon cancer before 2003, 493 704 men and 502 139 women of all ages and 177 787 men and 180 034 women ≥40 years old and without colon cancer were followed from January 1, 2003 to December 31, 2005.

Statistical analyses

Age, diabetes status, diabetes duration, and other covariates present in the reimbursement databases were determined as a status or a diagnosis on or before January 1, 2003. Colon cancer was only counted in cases in which the incidence occurred within the 3-year period from January 1, 2003 to December 31, 2005.

To compare whether the diabetes patients had a higher probability of receiving an examination to detect potential colon cancer than subjects without diabetes, the following examinations were performed by the χ^2 test: i) abdominal sonography; ii) computed tomography and/or magnetic resonance imaging; iii) colofibroscopy; iv) tumor markers including carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, CA-125, CA-153, and antisquamous cell carcinoma antigen; and v) any of the above.

Multivariable Cox regression models were created first to calculate the adjusted RRs for the following independent variables (diabetes/metformin status models): age, sex, diabetes status (yes vs no), dyslipidemia (ICD-9-CM codes: 272.0–272.4), obesity (278), hypertension (401–405), chronic obstructive pulmonary disease (COPD, 490–496, a surrogate for smoking), asthma (493), stroke (430–438), nephropathy (580–589), ischemic heart disease (410–414), peripheral arterial disease (250.7, 785.4, 443.81, and 440–448), eye disease (250.5, 362.0, 369, 366.41, and 365.44), statins, fibrates, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, calcium channel blockers, aspirin, dipyridamole, clopidogrel/ticlopidine, nonsteroidal anti-inflammatory drugs (NSAID), sulfonylurea, metformin, insulin (nonusers, users <3 years, and users ≥3 years), acarbose, thiazolidinedione, region of residence, occupation, and potential colon cancer detection examinations. The region of residence, classified as Taipei, Northern, Central, Southern, and Kao-Ping/Eastern regions, served as a surrogate for geographical distribution of environmental exposure. Insured individuals were classified according to their occupation (a surrogate for socioeconomic status) as class I (civil servants, teachers, employees of governmental or private businesses, professionals, and technicians), class II (people without a specific employer, self-employed people, or seamen), class III (farmers or fishermen), and class IV (low-income families supported by social welfare or veterans).

To evaluate whether diabetes duration affected the RR, the independent variable of 'diabetes status' in the above 'diabetes/metformin status models' was re-categorized as 'no diabetes' (the referent group) and diabetes duration for <1, 1–3, and ≥3 years (diabetes duration models). To evaluate whether there was an association between metformin use and colon cancer risk, the duration of metformin use was categorized as <1, 1–3, and ≥3 years and the RR was compared with nonusers (metformin duration models). The other covariates entered into these regression models were the same as those in the 'diabetes/metformin status model'.

As smoking may also increase the risk of colon cancer (27), and a recent animal study suggested that metformin can prevent lung cancer induced by the tobacco carcinogen in A/J mice (28), we attempted to analyze whether metformin use would reduce or modify the risk of colon cancer associated with tobacco use by using COPD as a surrogate for smoking. Multivariable models were created to estimate the adjusted RRs for the joint effect of metformin use and COPD (metformin/COPD joint effect models) by dividing the subjects into four subgroups: i) group 1, metformin use (+)/COPD (−) (referent group); ii) group 2, metformin use (+)/COPD (+); iii) group 3, metformin use (−)/COPD (−); and iv) group 4, metformin use (−)/COPD (+). Interaction between metformin use and COPD was then assessed by adding the cross-product term in the models and determining the statistical significance of the coefficient for the interaction term (metformin/COPD interaction models). The other independent variables entered into these models were the same as in the previous 'diabetes/metformin status model'.

Analyses were conducted using SAS Statistical Software, version 9.1 (SAS Institute, Cary, NC, USA). A P value <0.05 was considered statistically significant.

Results

Table 1 compares the performance of clinical examinations that might potentially lead to the incident detection of colon cancer in diabetes patients and subjects without diabetes. The diabetes patients had a significantly higher probability of receiving clinical examinations that might potentially lead to the detection of colon cancer.

Table 2 shows the multivariable-adjusted RRs for colon cancer with regard to different independent variables in the 'diabetes/metformin status models'. Age, male sex, diabetes, COPD, ischemic heart disease, dyslipidemia, metformin, region of residence, and potential colon cancer detection examinations were significant predictors in either the model for all ages or age ≥40 years. Nephropathy and NSAID users had a significantly higher risk for all ages, but the risk was not significant for subjects aged ≥40 years.

Table 3 shows the additional Cox models. In the 'diabetes duration models', only those with new-onset diabetes (<1 year) and those with diabetes for ≥3 years had significantly higher risk of colon cancer. In the 'metformin duration models', even though an inverse

Table 1 Comparison of examinations potentially leading to an incident diagnosis of colon cancer, in Taiwanese patients with and without diabetes mellitus, for all ages and age ≥40 years.

	Diabetes mellitus				
	No		Yes		
Examination	*n*	Percentage (%)	*n*	Percentage (%)	***P* value**
Abdominal sonography					
All ages					
No	828 952	89.45	97 735	10.55	<0.0001
Yes	52 349	75.67	16 832	24.33	
Age ≥40 years					
No	280 988	77.33	82 389	22.67	<0.0001
Yes	31 540	67.69	15 054	32.31	
CT/MRI					
All ages					
No	880 994	88.50	114 449	11.50	<0.0001
Yes	307	72.24	118	27.76	
Age ≥40 years					
No	312 304	76.24	97 336	23.76	0.0003
Yes	224	67.67	107	32.33	
Colofibroscopy					
All ages					
No	868 008	88.93	108 039	11.07	<0.0001
Yes	13 293	67.07	6528	32.93	
Age ≥40 years					
No	302 433	76.82	91 277	23.18	<0.0001
Yes	10 095	62.08	6166	37.92	
Tumor markers					
All ages					
No	871 837	88.60	112 163	11.40	<0.0001
Yes	9464	79.74	2404	20.26	
Age ≥40 years					
No	307 924	76.31	95 615	23.69	<0.0001
Yes	4604	71.58	1828	28.42	
Any of the above					
All ages					
No	811 621	89.86	91 617	10.14	<0.0001
Yes	69 680	75.22	22 950	24.78	
Age ≥40 years					
No	270 335	77.83	77 005	22.17	<0.0001
Yes	42 193	67.37	20 438	32.63	

CT, computed tomography; MRI, magnetic resonance imaging.

trend was observed in the risk of colon cancer with a longer duration of metformin use, only users for ≥3 years would have a significantly lower risk of ∼35%. In the 'metformin/COPD joint effect models', when compared with the referent group (those who used metformin and did not have COPD), the risk was only significantly higher for those who did not use metformin and had COPD simultaneously. For those who used metformin, the risk was not significantly different between patients with and without COPD. The *P* value for the interaction term was not significant ($P>0.1$) in the 'metformin/COPD interaction model' either for all ages or for those aged ≥40 years (data not shown).

Discussion

This study showed that even though patients with diabetes may have a higher probability of receiving examinations that could lead to an incident detection of colon cancer (Table 1), as reported by Lewis *et al.* (25), the risk of colon cancer in patients with diabetes remained significantly higher than that in the subjects without diabetes in the Cox regression analyses, after adjustment for confounders and these examinations (Table 2). Furthermore, metformin use was consistently associated with a lower risk of colon cancer (Tables 2 and 3), especially with use for ≥3 years (Table 3). The use of metformin also reduced the risk of colon cancer related to smoking when COPD was used as a surrogate (Table 3), but there was no significant interaction between metformin use and COPD on colon cancer risk.

Diabetes was not the only chronic disease linked to colon cancer; a variety of comorbidities such as COPD (a surrogate for smoking), nephropathy, ischemic heart disease, and dyslipidemia were also associated with a higher risk for colon cancer (Table 2). This strongly suggested that the common pathological changes

Table 2 Adjusted relative risks for colon cancer derived from Cox proportional hazard regression in the 'diabetes/metformin status models'.

			All ages				Age ≥40 years		
Variables	**Interpretation**	**Colon cancer cases** (*n*)	RR	95% CI	*P* value	**Colon cancer cases** (*n*)	RR	95% CI	*P* value
Age	Every 1-year increment	2389	1.055	(1.052, 1.058)	<0.0001	2029	1.042	(1.038, 1.046)	<0.0001
Sex	Men vs women	1296/1093	1.286	(1.185, 1.396)	<0.0001	1104/925	1.270	(1.162, 1.389)	<0.0001
Diabetes	Yes vs no	678/1711	1.243	(1.105, 1.399)	0.0003	658/1371	1.274	(1.129, 1.437)	<0.0001
Hypertension	Yes vs no	943/1446	0.903	(0.805, 1.013)	0.0828	931/1098	0.949	(0.844, 1.067)	0.3848
COPD	Yes vs no	843/1546	1.214	(1.093, 1.349)	0.0003	779/1250	1.231	(1.102, 1.375)	0.0002
Asthma	Yes vs no	320/2069	0.930	(0.809, 1.069)	0.3063	299/1730	0.965	(0.835, 1.115)	0.6274
Stroke	Yes vs no	362/2027	0.960	(0.845, 1.091)	0.5351	358/1671	1.018	(0.894, 1.159)	0.7886
Nephropathy	Yes vs no	283/2106	1.148	(1.007, 1.309)	0.0385	262/1767	1.123	(0.980, 1.286)	0.0952
Ischemic heart disease	Yes vs no	608/1781	1.179	(1.050, 1.324)	0.0054	595/1434	1.197	(1.064, 1.347)	0.0028
Peripheral arterial disease	Yes vs no	203/2186	1.125	(0.966, 1.311)	0.1297	197/1832	1.131	(0.969, 1.321)	0.1197
Eye disease	Yes vs no	75/2314	1.097	(0.848, 1.417)	0.4812	75/1954	1.146	(0.885, 1.484)	0.2999
Dyslipidemia	Yes vs no	552/1837	1.213	(1.079, 1.363)	0.0012	528/1501	1.161	(1.030, 1.309)	0.0146
Obesity	Yes vs no	14/2375	0.992	(0.586, 1.681)	0.9777	9/2020	0.708	(0.367, 1.365)	0.3029
Statin	Yes vs no	202/2187	1.043	(0.884, 1.231)	0.6146	198/1831	1.056	(0.893, 1.248)	0.5246
Fibrate	Yes vs no	202/2187	0.915	(0.778, 1.076)	0.2817	196/1833	0.901	(0.764, 1.062)	0.2129
ACE inhibitor/ ARB	Yes vs no	270/2119	1.075	(0.921, 1.255)	0.3566	269/1760	1.071	(0.917, 1.250)	0.3877
Calcium channel blocker	Yes vs no	270/2119	1.039	(0.891, 1.211)	0.6259	270/1759	1.044	(0.895, 1.218)	0.5835
Aspirin	Yes vs no	657/1732	1.017	(0.912, 1.133)	0.7633	614/1415	1.034	(0.922, 1.161)	0.5649
Dipyridamole	Yes vs no	597/1792	0.961	(0.857, 1.078)	0.4986	584/1445	0.990	(0.881, 1.112)	0.8635
Clopidogrel/ ticlopidine	Yes vs no	47/2342	0.901	(0.669, 1.215)	0.4955	47/1982	0.923	(0.685, 1.244)	0.8986
NSAID	Yes vs no	2272/117	1.371	(1.133, 1.659)	0.0012	1930/99	1.139	(0.925, 1.402)	0.2193
Sulfonylurea	Yes vs no	274/2115	1.048	(0.849, 1.293)	0.6642	267/1762	1.007	(0.812, 1.248)	0.9517
Metformin	Yes vs no	206/2183	0.731	(0.580, 0.921)	0.0078	203/1826	0.739	(0.584, 0.934)	0.0115
Insulin	<3 years vs no	17/2364	0.909	(0.553, 1.495)	0.7067	17/2004	0.909	(0.552, 1.497)	0.7082
	≥3 years vs no	8/2364	1.729	(0.853, 3.505)	0.1290	8/2004	1.657	(0.816, 3.365)	0.1627
Acarbose	Yes vs no	27/2362	1.255	(0.827, 1.906)	0.2863	27/2002	1.258	(0.828, 1.912)	0.2819
Pioglitazone	Yes vs no	3/2386	0.784	(0.247, 2.494)	0.6808	3/2026	0.789	(0.248, 2.509)	0.6885
Rosiglitazone	Yes vs no	29/2360	1.218	(0.808, 1.838)	0.3460	29/2000	1.202	(0.797, 1.814)	0.3803
Region of residence	Northern vs Taipei	446/1041	1.118	(0.998, 1.252)	0.0536	362/858	1.108	(0.977, 1.256)	0.1112
	Central vs Taipei	306/1041	0.576	(0.505, 0.656)	<0.0001	261/858	0.583	(0.505, 0.673)	<0.0001
	Southern vs Taipei	309/1041	0.651	(0.569, 0.745)	<0.0001	285/858	0.695	(0.602, 0.802)	<0.0001
	Kao-Ping/ Eastern vs Taipei	287/1041	0.528	(0.462, 0.604)	<0.0001	263/858	0.563	(0.488, 0.648)	<0.0001
Occupation	II vs I	384/909	1.124	(0.998, 1.268)	0.0549	328/679	1.044	(0.914, 1.192)	0.5273
	III vs I	531/909	1.075	(0.953, 1.212)	0.2424	503/679	1.110	(0.976, 1.262)	0.1116
	IV vs I	565/909	0.983	(0.879, 1.098)	0.7575	519/679	1.048	(0.929, 1.182)	0.4479
Potential colon cancer detection examinations	Yes vs no	642/1747	1.884	(1.714, 2.071)	<0.0001	557/1472	1.715	(1.549, 1.898)	<0.0001

RR, relative risk; CI, confidence interval; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; refer to Materials and methods section for the categories of occupation.

associated with these conditions, such as insulin resistance, hyperinsulinemia, oxidative stress, and pro-inflammatory state, may underline the development of colon cancer. The link with these chronic comorbidities also suggested a complicated scenario in the study of the link between diabetes and colon cancer because at different diabetes stages these comorbidities may set in and influence the association. These comorbidities should also be considered and adjusted for in future studies evaluating the risk of developing colon cancer.

The ~30% higher risk of developing colon cancer associated with new-onset diabetes (diabetes duration

Table 3 Additional Cox proportional hazard regression models for relative risk for colon cancer. Only the relative risks for diabetes durations, duration of metformin use, and the joint effect of metformin use and COPD in the above models are shown. The other variables adjusted are the same as that shown in the 'diabetes/metformin status models' in Table 2.

			All ages				Age ≥40 years		
Variables	**Interpretation**	***n/N***	RR	95% CI	*P* value	***n/N***	RR	95% CI	*P* value
Diabetes duration models									
Diabetes duration	No diabetes	1711/907852	1.000			1371/285130	1.000		
	<1 year	66/9380	1.308	(1.020, 1.679)	0.0347	65/7228	1.349	(1.049, 1.736)	0.0197
	1–3 years	123/19569	1.087	(0.900, 1.313)	0.3844	119/15375	1.101	(0.908, 1.334)	0.3279
	≥3 years	489/59042	1.185	(1.055, 1.330)	0.0042	474/50088	1.193	(1.060, 1.344)	0.0036
Metformin duration models									
Metformin duration	Nonusers	472/61009	1.000			455/47538	1.000		
	<1 year	29/3973	0.876	(0.590, 1.301)	0.5109	29/3508	0.896	(0.603, 1.333)	0.5893
	1–3 years	56/7229	0.859	(0.629, 1.173)	0.3396	54/6516	0.843	(0.613, 1.159)	0.2933
	≥3 years	121/15780	0.643	(0.490, 0.845)	0.0015	120/15129	0.646	(0.490, 0.852)	0.0020
Metformin/ COPD joint effect models									
Metformin/ COPD	Metformin (+) /COPD (−)	114/17659	1.000			111/16152	1.000		
	Metformin (+) /COPD (+)	92/9323	1.086	(0.820, 1.438)	0.5660	92/9001	1.124	(0.847, 1.492)	0.4181
	Metformin (−) /COPD (−)	1432/807170	1.248	(0.955, 1.632)	0.1046	1139/255242	1.241	(0.944, 1.632)	0.1214
	Metformin (−) /COPD (+)	751/161691	1.548	(1.176, 2.036)	0.0018	687/77426	1.560	(1.178, 2.065)	0.0019

n, number of cases of colon cancer; *N*, number of cases followed; RR, relative risk; CI, confidence interval. The *P* value for the interaction term of metformin and COPD was not significant ($P>0.1$) in the 'metformin/COPD interaction model' for either all ages or age ≥40 years.

<1 year), as shown in the 'diabetes duration models' of Table 3, may argue against a causal role of diabetes in the development of colon cancer in these patients due to the brevity of the diabetes period. Detection bias might play some role during this time and a reverse causality of abnormal glucose metabolism induced by colon cancer could not be excluded. However, this might also indicate a link between prediabetes and colon cancer as the presence of insulin resistance with hyperinsulinemia before the onset of diabetes may significantly increase the risk of cancer (7, 8). The ~20% higher risk of colon cancer associated with diabetes for ≥3 years in the 'diabetes duration models' (Table 3) suggested a potential causal link with diabetes in these patients, as the diabetes was diagnosed at least 3 years before the colon cancer and would probably not be a consequence of the carcinogenic process.

The use of insulin (12), insulin secretagogues (13, 14, 15), or thiazolidinedione (19, 20) may also affect cancer risk. In this study, except for metformin, we could not identify any significant association with other antidiabetic therapies and colon cancer (Table 2). However, though not statistically significant, the use of insulin for ≥3 years was associated with a more than 60% higher risk of colon cancer (Table 2). Further in-depth analyses would be worthwhile to explore this insulin effect on colon cancer. The lower risk of colon cancer associated with metformin use (Tables 2 and 3) was in agreement with the earlier meta-analyses (19, 21) and supported the preliminary clinical trial by Hosono *et al.* (22). Together, these studies provided a strong rationale for undertaking larger clinical trials to investigate the cancer-protecting effects of metformin on various human malignancies including colon cancer (23, 24).

The higher risk of colon cancer associated with NSAID use in the analyses carried out for all ages (Table 2) probably reflected a preexisting higher inflammatory condition associated with their use. However, this association was not significant when the analyses were conducted for those aged ≥40 years (Table 2). We did not carry out in-depth analyses for the role of these drugs because it was not the main theme of this study.

Living in the Northern or Metropolitan Taipei region (the two most urbanized regions in Taiwan) was associated with a significantly higher risk of colon cancer than was living in other regions. This was compatible with the common concept that colon cancer is a disease related to a Westernized lifestyle (5). On the other hand, occupation was not significantly associated with colon cancer risk. This implied that socioeconomic status or income might not be a significant risk factor. As cancer is associated with a severe morbidity and most medical copayments can be waived for those insured with NHI, it was unlikely that there would be different detection rates among the social classes.

This study has several strengths. It is a population-based study with a large and nationally representative sample. Therefore, the findings of this study can be generalized to the population of Taiwan. However, generalization of the study findings to other ethnicities should be reconfirmed. The database included outpatients and inpatients, and we included diagnoses of both sets of patients. The use of medical records reduced the bias related to self-reporting. Finally, we excluded patients with type 1 diabetes to demonstrate a link with T2DM.

This study also has a few limitations. We did not have biochemical data such as glucose, insulin, HbA1c, or lipid levels to evaluate their potential effects. Some potential confounders such as anthropometric factors, dietary factors, physical activity, family history, and genetic parameters were not measured, and we used COPD as a surrogate for smoking. As this is an observational study, an experimental design will be needed to confirm the protective effect of metformin use on the development of colon cancer.

In summary, this study confirms a higher risk of colon cancer in patients with T2DM despite the existence of a detection bias. Furthermore, the results support that a protective effect of metformin on the development of colon cancer, and metformin use may protect against the colon cancer associated with smoking when COPD is used as a surrogate marker.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

C-H Tseng researched the data and wrote the manuscript.

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