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Original Research

Impact of detection bias on the risk of gastrointestinal cancer and its subsites in type 2 diabetes mellitus



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Abstract Background: Type 2 diabetes mellitus (T2DM) may be a risk factor for gastrointestinal (GI) cancers, but variations in study designs of observational studies may have yielded biased results due to detection bias. Furthermore, differences in risk for GI cancer subsites

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mellitus;
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have not been extensively evaluated. We aimed to determine the risk of GI cancer and its subsites in patients with T2DM and how it is affected by detection bias.

Methods: A matched cohort study was performed using the NCR-PHARMO database. New-users of ≥ 1 non-insulin anti-diabetic drug during 1998–2011 were matched with non-diabetic controls by year of birth, sex, and time between database entry and index. Cox regression analyses were performed with and without lag-period to estimate hazard ratios (HRs) for GI cancer and its subsites. Covariables included age, sex, use of other drugs and history of hospitalisation.

Results: An increased risk of GI cancer was observed in T2DM patients (HR 1.5, 95% confidence interval [CI] 1.3–1.7) compared with controls, which was attenuated in the 1-year lagged analysis (HR 1.4, 95% CI 1.2–1.7). Stratified by subsite, statistically significant increased risks of pancreatic (HR 4.7, 95% CI 3.1–7.2), extrahepatic bile duct (HR 4.2, 95% CI 1.5–11.8) and distal colon cancer (HR 1.5, 95% CI 1.1–2.1) were found, which remained statistically significantly increased in the lagged analysis.

Conclusions: T2DM patients had a 40% increased risk of GI cancer. Increased GI cancer risks tended to be weaker when reducing detection bias by applying a 1-year lag-period. Future observational studies should therefore include sensitivity analyses in which this bias is minimised.

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1. Background

Gastrointestinal (GI) cancers, encompassing malignancies of the gut, from the oesophagus till the anus; including the liver, gallbladder, extrahepatic bile ducts and the pancreas, are among the most common and lethal malignant neoplasms. In 2015, almost 25% of the total cancer incidence, and a third of the total cancer mortality in the Netherlands was due to a GI cancer [1]. Furthermore, data from the Netherlands Cancer Registry (NCR) indicate incidences of these cancers are rising [1].

Previous studies using NCR data have shown a higher prevalence of type 2 diabetes mellitus (T2DM) in patients with various GI cancers [2,3]. Indeed, a growing body of evidence suggests that T2DM may be a risk factor for the development of GI cancers (Table 1) [4–13]. The strongest associations have been described for liver and pancreatic cancer, with both a two-fold increased risk [14,15]. In addition, a 15%–30% increased risk has been reported for colorectal cancer [16–18]. With 830,000 individuals living in the Netherlands with diabetes mellitus in 2011 (of which $\pm 90\%$ with T2DM), diabetes mellitus poses a highly prevalent and potentially modifiable risk factor for GI cancer development [19]. There has been much discussion about whether previously reported associations in observational studies present an underlying biological mechanism between T2DM and cancer or represent detection bias or even reverse causality. These biases could have been the result of a diagnostic (protopathic) bias, i.e. an increased odds of detecting cancer shortly after the onset of diabetes, or by specific GI cancers inducing disturbances in glucose homeostasis [20,21].

To address this form of methodologic bias, a lag time between disease onset and the start of follow-up for cancer outcomes can be considered [22].

Furthermore, epidemiologic studies have shown that risk factors of GI cancer may vary within specific GI cancer anatomic subsites or histologic subtypes [23,24]. For instance, different risk factors have been identified for oesophageal squamous cell carcinoma and adenocarcinoma, and also for proximal and distal gastric cancer [23]. Up to now, data on subsite-specific risks of GI cancer in patients with T2DM are limited [25].

Therefore, our primary aim was to determine the overall risk of GI cancer in patients with T2DM, and explore the effects of detection bias/reverse causality on the association between T2DM and risk of GI cancer. Second, we stratified these analyses for specific GI cancer subsites/subtypes.

2. Methods

2.1. Data source

Data for this population-based cohort study were obtained from the PHARMO Database Network and linked at the individual patient level to the Eindhoven area of the NCR. The construct and validity of the linked database have been described elsewhere [26]. Data from the Eindhoven area of the NCR, maintained by the Netherlands Comprehensive Cancer Organisation, cover a demographic region with approximately 2.4 million inhabitants ($\sim 15\%$ of the Dutch population) and no academic hospitals. Trained registration clerks actively collect data on diagnosis, patient characteristics, staging and initial treatment from hospital medical

Table 1

Overview of GI cancer risk in patients with type 2 diabetes mellitus in meta-analyses of cohort studies.

Author (Ref.)	Oesophageal cancer	Gastric cancer	Colorectal cancer	Liver cancer	Bile duct cancer	Pancreatic cancer
Larsson <i>et al.</i> , 2005 [16]			RR 1.30 (1.20–1.40)			
Huang <i>et al.</i> , 2012 [9]	SRR 1.30 (1.12–1.50)					
Ge <i>et al.</i> , 2011 [10]		SRR 1.09 (0.98–1.22)				
Ren <i>et al.</i> , 2011 [13]					GB: SRR 1.52 (1.26–1.84)	
Ben <i>et al.</i> , 2011 [14]						SRR 1.95 (1.66–2.28)
Jiang <i>et al.</i> , 2011 [12]			SRR 1.27 (1.21–1.34)			
Jing <i>et al.</i> , 2012 [11]				ICC: SRR 1.97 (1.57–2.46)	ECC: SRR 1.63 (1.29–2.05)	
Wang <i>et al.</i> , 2012 [15]				HCC: SRR 2.31 (1.87–2.84)		
Deng <i>et al.</i> , 2012 [17]			RR 1.26 (1.20–1.31)			
Wu <i>et al.</i> , 2013 [8]			RR 1.22 (1.19–1.26)			

Abbreviations: ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; HR, hazard ratio; GB, gallbladder; ICC, intrahepatic cholangiocarcinoma; Ref, reference number; RR, relative risk; SRR, summary relative risk.

records. Vital status is obtained by linkage to Dutch municipal records.

The PHARMO Database Network is a large, patient-centric data network including linked observational databases designed for drug safety and outcomes research. For this study the Out-patient (community) Pharmacy Database was used, which contains longitudinal drug dispensing records, and included information on dispensing date, dose descriptions and amount dispensed. All drugs are coded according to their Anatomical Therapeutic Chemical/Defined Daily Dose Classification code [27]. Both the NCR and the PHARMO Database Network are recognised as high-quality data sources for (pharmaco-) epidemiological research that have collected information in overlapping regions in the Netherlands for a period of over 10 years [26].

2.2. Population and study design

We selected all individuals aged 30 years and older who received at least one anti-diabetic drug (ADD) prescription (ATC code ‘A10A’ or ‘A10B’) in the NCR-PHARMO database between 1 January 1998 and 31 December 2011. These subjects were classified as potential T2DM patients and the first prescription for an ADD defined their start of follow-up (index date). A random sample of subjects who never received ADDs during the study period was extracted from the database and classified as non-diabetic controls (Fig. 1).

Next, non-diabetic controls were matched to a T2DM patient by year of birth, sex and the time between database entry and the index date (± 90 days). Non-diabetic controls were assigned the same index date as their matched T2DM patients. For T2DM patients with more than one matched control the most optimal control was selected based on highest similarity of matching parameters, yielding a 1:1 matched cohort.

Potential T2DM patients who initiated ADD treatment with insulin or an insulin analogue (ATC code ‘A10A’) were excluded to minimise the amount of people with type 1 diabetes mellitus being misclassified as T2DM. All study subjects with a history of GI cancer before the index date were excluded. Furthermore, we excluded all prevalent ADD-users, i.e. T2DM patients without a minimum of 1 year of ADD-free follow-up in the NCR-PHARMO database before the index date. In addition, all individuals matched to excluded subjects were excluded as well. Individuals were followed from the index date until the first occurrence of a GI cancer, death from any cause, migration out of the PHARMO catchment area or end of data collection, whichever came first.

2.3. Outcomes

GI cancers were classified according to the International Classification of Diseases of oncology [28]. These included ‘any GI cancer’ (C15–26, excluding anal cancer), oesophageal cancer (C15), gastric cancer (C16), small intestinal cancer (C17), colon cancer (C18), rectal cancer (C19–20), hepatic cancer (C22), biliary tract cancer (C23: gallbladder, and C24: extrahepatic bile duct cancer) and pancreatic cancer (C25). In addition, stratified analyses were performed by sublocalisation of GI cancer sites (see [Supplementary Table 1](#) for sublocalisations). For the site-specific analyses, subjects were followed until the first-occurrence of the site-specific GI cancer event, despite other types of GI cancers occurring during follow-up.

2.4. Covariables

Both time-fixed and time-dependent covariables were considered as confounders based on the existing

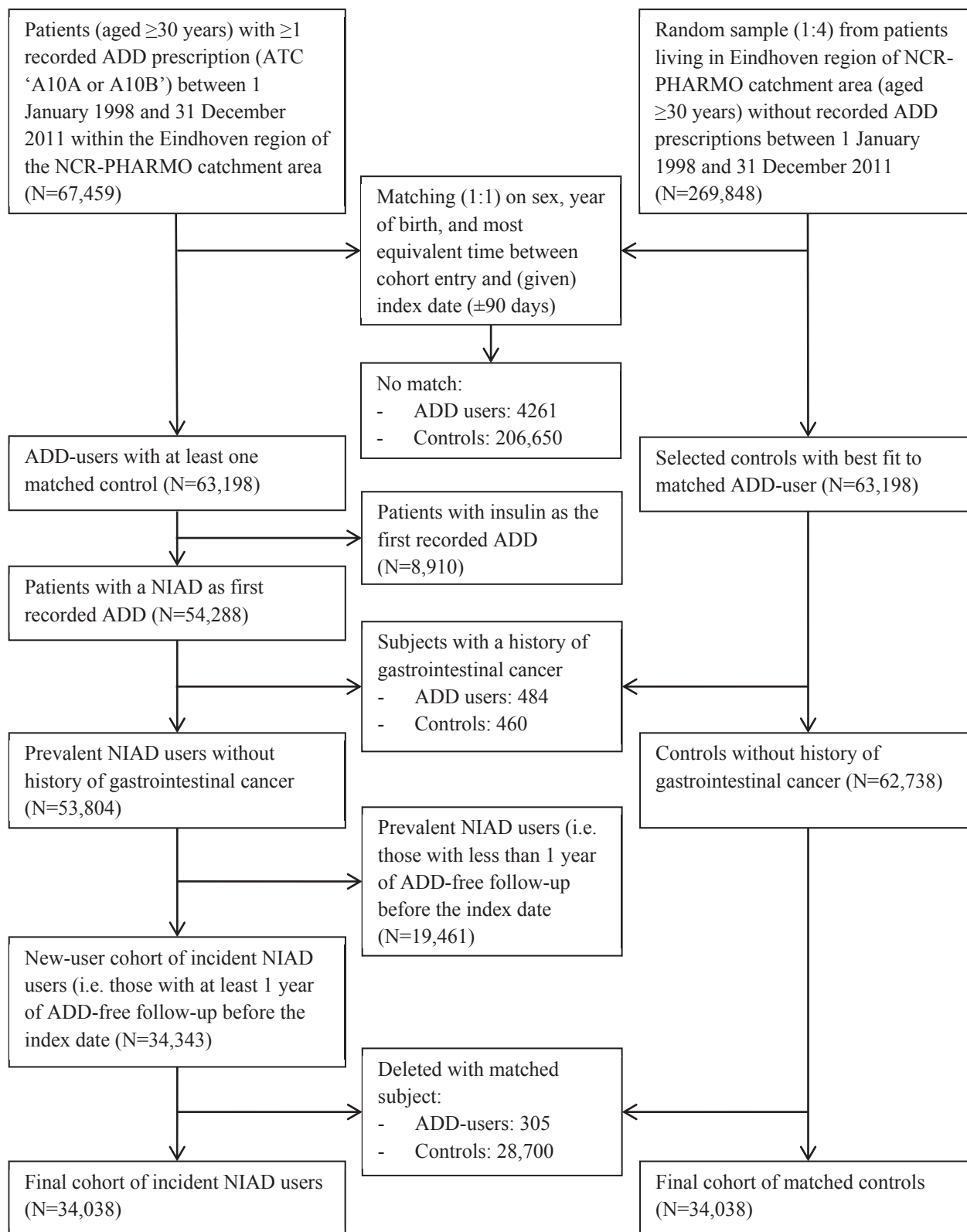


Fig. 1. Flow-chart of study population. Abbreviations: ADD, anti-diabetic drug; ATC, Anatomical Therapeutic Classification; NCR, Netherlands Cancer Registration; NIAD, non-insulin anti-diabetic drug.

literature. As time-fixed covariables sex and the number of hospitalisations before the index date (hospitalisation categories 0 or ≥1) were considered. Time-dependent covariables were determined at the start of

every 90-day time-period and included: age, the duration of diabetes in years (time since first recorded NIAD prescription), the use of other drugs known to impact GI cancer risk in the 90 days before the start of each

interval (statins, aspirin, non-aspirin non-steroidal anti-inflammatory drugs, proton pump inhibitors (PPIs), bisphosphonates, tamoxifen and oral contraceptives). In addition, the use of *Helicobacter pylori* eradication therapy was used as a proxy-indicator for *Helicobacter pylori* infection (see [Supplementary Table 2](#) for ATC codes).

2.5. Statistical analyses

Differences in demographic and clinical characteristics at baseline between T2DM patients and matched controls were compared using chi-squared test for categorical variables and Student's t-test for continuous variables. Incidence rates (IR) of GI cancer for every (sub)group were calculated by dividing the number of GI cancer events by the total amount of person-years of follow-up (for the IR of GI cancers by tumour stage see [Supplementary Table 3](#)).

Cox proportional hazards analysis was used to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of GI cancer in T2DM patients versus matched controls. Stratified analyses were performed by sex, for specific GI cancer sites and for subsites of specific GI cancer sites. Covariables were entered into the final model if they changed the beta coefficient of the primary exposure variable by more than 5%. Detection bias after the onset of T2DM was reduced by repeating the overall analyses with a lag-period of 1 year. The lag-period implied censoring a subject on the date of cancer diagnosis if the cancer occurred during the first year of follow-up.

2.6. Sensitivity analysis

To further explore the effects of reducing detection bias, we preformed sensitivity analyses in which we repeated the 1-year lagged analyses as described previously with a lag-period of three years instead. All data management and analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

In both T2DM patients and non-diabetic controls, the mean age at baseline was 63.9 years, and 51% of subjects were males ([Table 2](#)). There were no differences seen between the age and sex distribution at baseline. After at least 1 year of ADD-free follow-up, most incident ADD users initiated treatment with metformin (73.8%) and/or sulfonylureas (28.0%). Statistically significant differences were observed for the use of various other drugs during the 90 days before the start of follow-up, with the largest differences seen for prior use of statins, anti-hypertensives and PPIs. In addition, T2DM patients were more often hospitalised before the index date (51.7% versus 38.5%).

3.2. Risk of GI cancer overall

Generally, an increased risk of GI cancer was observed in patients with T2DM compared with non-diabetic controls (Adj. HR 1.5, 95% CI 1.3–1.7; [Table 3](#)),

Table 2
Baseline characteristics of type 2 diabetic patients and matched non-diabetic controls.

Characteristic	Type 2 diabetic (n = 34,038)		Non-diabetic (n = 34,038)		p-value ^a
Age (years; mean, SD)	63.9	12.6	63.9	12.6	1.00
Sex (n, % male)	17,343	51	17,343	51	1.00
Use of anti-diabetic drugs^b (n, %)					
Metformin	25,115	73.8			
Sulfonylureas	9536	28.0			
Thiazolidinediones	388	1.1			
Meglitinides	38	0.1			
Incretins	66	0.2			
Use of other drugs (n, %)					
Anti-hypertensives	20,667	60.7	9495	27.9	<0.01
Aspirin	6156	18.1	3080	9.1	<0.01
Bisphosphonates	1112	3.3	812	2.4	<0.01
<i>H. pylori</i> eradication therapy	40	0.1	24	0.1	0.05
Non-aspirin NSAIDs	5171	15.2	3324	9.8	<0.01
Proton pump inhibitors	6795	20.0	3268	9.6	<0.01
Statins	13,396	39.4	4529	13.3	<0.01
History of hospitalisations (n, %)					
0 hospitalisations	16,450	48.3	20,932	61.5	<0.01
≥1 hospitalisations	17,588	51.7	13,106	38.5	

Abbreviations: *H. pylori*, *Helicobacter pylori*; NSAIDs, non-steroidal anti-inflammatory drugs.

^a p-value based on Student's t-test for continuous variables and chi-squared test for categorical variables.

^b During 90 days before the index date.

Table 3

Risk of GI cancer in patients with type 2 diabetes mellitus and matched non-diabetic controls, by specific GI cancer site.

Cancer site					Age-sex adjusted				Fully adjusted			
	Non-diabetic		Type 2 diabetic		Overall		One-year lagged		Overall		One-year lagged	
	Events	IR ^a	Events	IR ^a	HR	95% CI	HR	95% CI	HR ^b	95% CI	HR ^b	95% CI
Any GI cancer	351	252	583	408	1.7*	1.5–1.9	1.7*	1.4–2.0	1.5*	1.3–1.7	1.4*	1.2–1.7
By cancer subsite												
Upper GI cancer	71	51	96	67	1.4*	1.0–1.9	1.7*	1.2–2.5	1.1	0.77–1.5	1.3	0.90–2.0
Oesophageal cancer	25	18	41	29	1.7*	1.0–2.8	2.3*	1.3–4.1	1.3 ^c	0.74–2.2	1.6 ^c	0.86–3.1
Gastric cancer	46	33	50	35	1.1	0.75–1.7	1.4	0.86–2.2	0.88	0.57–1.4	1.1	0.7–1.8
Small intestinal cancer	<5	1	6	4	2.9	0.58–14.3	1.5	0.2–8.7	^e	^e	^e	^e
Lower GI cancer	241	173	330	231	1.4*	1.2–1.7	1.4*	1.2–1.7	1.2	0.99–1.4	1.1	0.93–1.4
Colon cancer	168	120	253	176	1.6*	1.3–1.9	1.5*	1.2–1.9	1.4*	1.1–1.7	1.2	0.96–1.6
Rectal cancer	77	55	87	61	1.1	0.83–1.5	1.2	0.88–1.8	0.88	0.63–1.2	0.99	0.68–1.4
HPB cancer	39	28	156	109	4.0*	2.8–5.7	4.1*	2.5–6.5	4.4*	3.0–6.4	4.0*	2.4–6.7
Liver cancer	<5	1	15	10	7.4*	1.7–32.4	–	–	^e	^e	^e	^e
Biliary tract cancer	7	5	20	14	2.9*	1.2–6.7	3.5*	1.2–10.7	3.5 ^{d,*}	1.4–8.4	4.2 ^{d,*}	1.3–13.1
Pancreatic cancer	30	21	122	85	4.1*	2.7–6.1	3.5*	2.0–6.0	4.7*	3.1–7.2	3.6*	2.0–6.5

Abbreviations: CI, confidence interval; GI, gastrointestinal; HPB, hepato-pancreatico-biliary; HR, hazard ratio; IR, incidence rate.

*Statistically significant with $p < 0.05$.^a Per 100,000 person years.^b Adjusted for age, sex, use of statins, proton pump inhibitors, anti-hypertensives 90 days before start of each time-interval.^c Additionally adjusted for history of hospitalisation.^d Adjusted only for use of statins 90 days before the start of each interval.^e Fully adjusted analysis not possible due to insufficient events for additional covariate adjustments.

which remained statistically significant increased when applying a 1-year lag-period (Adj. HR 1.4, 95% CI 1.2–1.7). After stratification by GI cancer subsite, we observed a 4-fold increased risk of hepato-pancreatico-biliary (HPB) cancer (Adj. HR 4.4, 95% CI 3.0–6.4), but not for upper and lower GI cancer (Adj. HR 1.1, 95% CI 0.77–1.5 and Adj. HR 1.2, 95% CI 0.99–1.4, respectively). In the analysis that reduced detection bias (i.e. with the addition of a 1-year lag-period), a slightly attenuated risk of HPB cancer was seen (Adj. HR 4.0, 95% CI 2.4–6.7). When stratifying the analyses by sex, statistically significant increased risks of overall GI cancer and of lower GI cancer were seen in the 1-year lagged analyses in men (Adj. HR 1.6, 95% CI 1.2–1.9, and Adj. HR 1.3, 95% CI 1.0–1.8 respectively), but not in women (Table 4). Also, the increased risk of HPB cancer was more pronounced in men than in women.

3.3. Risk of specific GI cancer sites

After we had broken down our analyses by GI cancer site, we observed a statistically significant increased risk of colon cancer (Adj. HR 1.4, 95% CI 1.1–1.7), pancreatic cancer (Adj. HR 4.7, 95% CI 3.1–7.2) and biliary tract cancer (Adj. HR 3.5, 95% CI 1.4–8.4) in patients with T2DM compared with non-diabetic controls (Table 3). The latter two remained significantly increased in the 1-year lagged analysis (Adj. HR 3.6, 95% CI 2.0–6.5 and Adj. HR 4.2, 95% CI 1.3–13.1, respectively). However, no statistically significantly increased risk of pancreatic or biliary tract cancer was seen in the sensitivity analyses (Adj. HR 2.0, 95% CI

0.96–4.2 and Adj HR 8.1, 95% CI 0.95–68.8 respectively). In the sex-specific analyses, the increased risk of colon cancer confined to men, and the risk of pancreatic cancer was more pronounced in men (Table 4).

3.4. Risk of GI cancer subsites/subtypes

After stratifying the specific GI cancer sites by sub-localisation and subtype (Table 5), an increased risk in patients with T2DM was found for extrahepatic bile duct cancer (Adj. HR 4.2, 95% CI 1.5–11.8), and for distal colon cancer (HR 1.5, 95% CI 1.1–2.1), both of which remained statistically significantly raised after removal of detection bias. No significant differences were observed for other subsites of GI cancer. Also, we did not observe any significant differences for histologic subtypes of oesophageal cancer.

4. Discussion

We observed a 50% increased risk of GI cancer in patients with T2DM compared with non-diabetic controls. However, after accounting for potential detection bias this dropped to a 40% increased risk. The overall increased risk in T2DM patients was explained by a four-fold increased risk of HPB cancers, which was driven by pancreatic cancer (five-fold increase) and biliary tract cancer (four-fold increase). The risk of HPB and pancreatic cancer, but not biliary tract cancer, was attenuated following adjustment to minimise detection bias.

While several pathways have been proposed, including insulin resistance and fat-induced chronic

Table 4

Sex-specific risk of GI cancer in patients with type 2 diabetes mellitus and matched non-diabetic controls, by specific GI cancer site.

Cancer site					Age-sex adjusted				Fully adjusted			
	Non-diabetic		Type 2 diabetic		Overall		One-year lagged		Overall		One-year lagged	
	Events	IR ^a	Events	IR ^a	HR	95% CI	HR	95% CI	HR ^b	95% CI	HR ^b	95% CI
Men												
Any GI cancer	203	284	344	470	1.7*	1.5–2.1	1.8*	1.5–2.2	1.6*	1.3–1.9	1.6*	1.2–1.9
By cancer site												
Upper GI cancer	52	73	74	101	1.5*	1.0–2.1	1.9*	1.2–2.9	1.0	0.70–1.5	1.4	0.85–2.1
Oesophageal cancer	18	25	34	46	2.0*	1.1–3.5	3.2*	1.6–6.5	1.3 ^c	0.71–2.4	2.1 ^c	0.98–4.5
Gastric cancer	36	50	37	50	1.1	0.66–1.7	1.2	0.70–2.0	0.77	0.47–1.3	0.90	0.50–1.6
Small intestinal cancer	0	—	<5	5	—	—	—	—	—	—	—	—
Lower GI cancer	131	183	185	253	1.5*	1.2–1.8	1.5*	1.2–1.9	1.3*	1.0–1.7	1.3*	1.0–1.8
Colon cancer	85	119	139	189	1.7*	1.3–2.2	1.6*	1.2–2.2	1.6*	1.2–2.2	1.4*	1.0–2.0
Rectal cancer	49	68	54	73	1.1	0.75–1.6	1.3	0.87–2.2	0.91	0.59–1.4	1.2	0.72–1.9
HPB cancer	20	28	84	115	4.3*	2.6–6.9	4.5*	2.3–9.0	4.8*	2.9–8.1	4.5*	2.2–9.4
Liver cancer	0	—	10	14	—	—	—	—	—	—	—	—
Biliary tract cancer	<5	6	8	11	2.1*	0.62–6.9	2.7	0.51–13.8	3.0	0.86–10.2	4.0	0.75–21.4
Pancreatic cancer	16	22	67	91	4.2*	2.5–7.3	4.2*	2.0–9.1	5.0*	2.8–8.8	4.3*	1.9–9.8
Women												
Any GI cancer	148	218	239	343	1.6*	1.3–2.0	1.5*	1.2–1.9	1.4*	1.1–1.8	1.2	0.92–1.6
By cancer site												
Upper GI cancer	19	28	22	32	1.2	0.64–2.8	1.3	0.65–2.6	1.3	0.67–2.6	1.3	0.61–2.9
Oesophageal cancer	7	10	7	10	1.0	0.35–2.9	0.83	0.25–2.7	1.3	0.41–4.2	0.80	0.21–3.0
Gastric cancer	10	15	13	19	1.4	0.60–3.1	2.1	0.79–5.7	1.4	0.55–3.4	2.0	0.67–5.8
Small intestinal cancer	<5	3	<5	3	0.95	0.13–6.8	0.48	0.04–5.3	^c	^c	^c	^c
Lower GI cancer	110	162	145	208	1.3*	1.0–1.7	1.3	0.94–1.7	1.0	0.79–1.4	0.91	0.66–1.3
Colon cancer	80	122	114	163	1.4*	1.1–1.9	1.3	0.95–1.9	1.1	0.82–1.5	1.0	0.70–1.5
Rectal cancer	28	41	33	47	1.2	0.72–2.0	1.1	0.62–1.9	0.83	0.48–1.5	0.73	0.39–1.4
HPB cancer	19	28	72	103	3.7*	2.3–6.2	3.6*	1.9–7.1	4.0*	2.3–6.9	3.6*	1.8–7.4
Liver cancer	<5	3	5	7	2.5	0.48–12.7	—	—	^c	^c	^c	^c
Biliary tract cancer	<5	4	12	17	3.9*	1.1–13.9	4.4	0.96–20.6	4.2 ^{d,*}	1.1–15.6	4.5 ^{d,*}	0.93–22.0
Pancreatic cancer	14	21	55	78	3.9*	2.2–7.0	2.9*	1.3–6.1	4.5*	2.4–8.3	3.0*	1.3–6.9

Abbreviations: CI, confidence interval; GI, gastrointestinal; HPB, hepato-pancreatico-biliary; HR, hazard ratio; IR, incidence rate.

*Statistically significant with $p < 0.05$.^a Per 100,000 person-years.^b Adjusted for age, use of statins, proton pump inhibitors, anti-hypertensives 90 days prior to start of each time-interval.^c Additionally adjusted for history of hospitalisation.^d Adjusted only for use of statins 90 days prior to start of each interval.^e Fully adjusted analysis not possible due to insufficient events for additional covariate adjustments.

inflammation [5,29], the precise biological mechanisms by which T2DM increases the risk of GI cancer remains unclear. Insulin may promote carcinogenesis through the insulin receptor and insulin-like growth factor-receptor (IGF-R), which are overexpressed on various types of tumour cells [30]. Binding of these receptors by insulin activates the mTOR signalling pathway (mammalian target of rapamycin signalling pathway), resulting in abnormal cell proliferation, inhibition of apoptosis, angiogenesis and carcinogenesis [31]. Hyperinsulinemia may also predispose to carcinogenesis by indirectly increasing the production of IGF-1 via the liver, and by increasing the amount of bioavailable IGF-1 by decreasing the level of IGF-binding proteins [29].

The results of this study add to the current evidence from observational studies. In their meta-analyses of cohort studies, Ben *et al.* [14] found a two-fold increased risk of pancreatic cancer in newly diagnosed T2DM patients, and Ren *et al.* [13] observed a 1.4-fold

increased risk of extrahepatic biliary tract cancer. However, the potential for reverse causality is a primary concern for these cancers, as both can induce hyperglycemia or frank diabetes [32]. Our results may still be affected by an unknown degree of protopathic bias (reverse causality), as a 1-year lag-period may not be enough to exclude the effects of these cancers on the development of T2DM symptoms. Indeed, when increasing the lag-period to 3 years, no statistically significantly increased risks of pancreatic cancer and biliary tract cancer between T2DM patients and controls were observed (Adj. HR 2.0, 95% CI 0.96–4.8 and Adj. HR 8.1, 95% CI 0.95–68.8, respectively). However, this could also be explained by a lack of statistical power. Nonetheless, an increased risk of pancreatic cancer with longstanding T2DM (≥ 10 years) has been reported in the literature, suggesting that diabetes might still be a risk factor for pancreatic cancer development [14].

Table 5

Risk of GI cancer in patients with type 2 diabetes mellitus and matched non-diabetic controls, by GI cancer subsite.

Cancer site					Age-sex adjusted				Fully adjusted			
	Non-diabetic		Type 2 diabetic		Overall		One-year lagged		Overall		One-year lagged	
	Events	IR ^a	Events	IR ^a	HR	95% CI	HR	95% CI	HR ^b	95% CI	HR ^b	95% CI
Oesophageal cancer												
<i>By cancer subsite</i>												
Upper/middle oesophageal cancer	<5	2	7	5	2.3	0.59–8.8	1.9	0.49–7.8	^c	^c	^c	^c
Lower oesophageal cancer	21	15	32	22	1.6	0.92–2.8	2.5*	1.3–5.0	1.2 ^c	0.68–2.2	1.9 ^c	0.92–4.0
<i>By histologic subtype</i>												
Squamous cell carcinoma	7	5	10	7	1.4	0.54–3.7	1.6	0.52–4.9	^c	^c	^c	^c
Adenocarcinoma	17	12	29	20	1.8	0.99–3.3	2.7*	1.3–5.6	1.3	0.68–2.4	1.9	0.86–4.1
Gastric cancer												
<i>By cancer subsite</i>												
Proximal gastric cancer	20	14	21	15	1.1	0.59–2.0	1.2	0.59–2.4	0.89	0.46–1.7	0.97	0.45–2.1
Distal gastric cancer	10	7	11	8	1.2	0.51–2.9	1.8	0.68–4.6	^c	^c	^c	^c
Biliary tract cancer												
<i>By cancer subsite</i>												
Gallbladder cancer	<5	1	<5	3	2.0	0.36–10.9	2.0	0.18–21.6	^c	^c	^c	^c
Extrahepatic bile duct cancer	5	4	16	11	3.2*	1.2–8.7	4.1*	1.2–14.4	4.2 ^{d,*}	1.5–11.8	5.5 ^{d,*}	1.5–20.0
Colon cancer												
<i>By cancer subsite</i>												
Proximal colon cancer	90	64	136	95	1.6*	1.2–2.0	1.3	0.98–1.8	1.3	0.98–1.8	1.1	0.75–1.5
Distal colon cancer	71	51	112	78	1.6*	1.2–2.2	1.8*	1.3–2.5	1.5*	1.1–2.0	1.5*	1.1–2.2

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IR, incidence rate.

*Statistically significant with $p < 0.05$.^a Per 100,000 person-years.^b Adjusted for age, sex, use of statins, proton pump inhibitors, anti-hypertensives 90 days before start of each time-interval.^c Additionally adjusted for history of hospitalisation.^d Adjusted only for use of statins 90 days before each interval.^e Fully adjusted analysis not possible due to insufficient events for additional covariate adjustments.

An interesting finding in this study was the difference in risk between genders and distal and proximal colon cancer. We identified that men, but not women, with T2DM were at an increased risk of colon cancer. Varying differences in the risk of colorectal cancer have been reported in men and women with T2DM [25,33–35], and large meta-analyses of observational studies have reported moderate (20–30%) increased risks of colorectal cancer in both men and women [8,16,17,36–38]. With regards to colon cancer, three meta-analyses have reported increased risks of both proximal and distal colon cancer in patients with T2DM, with stronger risk estimates for proximal colon cancer [16,37,38]. However, differences in observed risks could result from variations in the definitions of proximal and distal colon cancer in the literature as it cannot always be defined from which part of the colon a tumour has originated.

In contrast to meta-analyses of cohort studies, we did not find a statistically significant increased risk of liver cancer in patients with T2DM. Wang *et al.* [15] reported a relative risk of 2.4 (95% CI 1.7–3.6) for hepatocellular carcinoma in T2DM patients, combining results from seven cohort studies. The most likely reason we could not replicate these findings is because

of a lack of statistical power for this cancer site. Similarly, we did not find an increased risk of specific upper GI cancer sites like oesophageal, gastric, and small intestinal cancer in our cohort. Moreover, when all sites were combined we also did not identify an increased risk of upper GI cancer. This adds to the current literature for the risk of upper GI cancers, such as oesophageal and gastric cancer, in patients with T2DM [6,39–42].

Our study has a number of limitations worth mentioning. First, we were not able to correct for several important general and cancer-specific risk factors, including obesity, smoking status, alcohol use, physical inactivity and high-caloric diet, which could have confounded the results. The majority of T2DM patients are obese, and obesity has been shown to be associated with and increased risk of GI cancers [43]. Moreover, visceral or abdominal fat is more metabolically active and therefore potentially more harmful than fat distributed at the hips [31]. Second, due to the relatively small size of the population and the matched design, a lack of statistical power existed for cancer sites, such as liver cancer and small intestinal cancer. This also resulted in a limited ability to statistically adjust for confounders in a multivariate analysis for

subsites of GI cancer. Although we acknowledge that propensity score adjustment would be an effective strategy to further reduce residual confounding and limit the number of covariates in the multivariate model [22], it cannot overcome the unmeasured confounding in the data source and therefore this strategy was not applied. Third, the subsite-specific analyses were of an exploratory nature rather than a hypothesis-testing one.

Fourth, T2DM patients were identified based on the use of anti-diabetic drugs, leading to potential misclassification of diet-controlled T2DM patients as controls. Also, included patients were required to have at least one drug prescription via their community pharmacy. Patients not registered at a pharmacy were therefore not included. Consequently, the control group may be sicker than the general population, which may have resulted in an elevated risk of GI cancer in this group. Ultimately, this would bias the risk ratio towards the null, yet we observed a statistically significant association between T2DM and GI cancer sites.

Finally, a causal relationship between T2DM and GI cancer cannot be proven in the present study. T2DM may function as a proxy indicator of several pathophysiologic mechanisms that, in turn, may promote cancer growth, such as insulin resistance, hyperglycemia, hyperinsulinemia, chronic inflammation and increase hormone levels.

The strengths of this study are provided by the use of the population-based linked NCR-PHARMO database, which guarantees a high level of cancer ascertainment and longitudinal information on drug exposure during follow-up. This prevents an overestimation of the number of (false positive) cancers, which may occur in studies using an insurance claims database or data from general practitioners without linking to some form of cancer registry or pathology database. In addition, the longitudinal nature of the PHARMO database provides reliable information on confounding drug exposures during follow-up; such as statins, non-steroidal anti-inflammatory drugs and PPIs.

In conclusion, following an adjustment for potential detection bias, T2DM was associated with a 40% increased risk of GI cancer, and a four-fold increased risk of pancreatic and biliary tract cancer. In particular, the strong associations found for HPB cancers and pancreatic cancer may be partly caused by an increased detection of these cancers in the first years after the onset of T2DM. Future studies investigating associations between T2DM and GI cancer should therefore always include a sensitivity analysis in which detection bias or reverse causality are kept to a minimum by including one or multiple years of lag-time.

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Conflict of interest statement

Myrthe van Herk-Sukel is an employee at PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands. This independent research institute financially supported studies for government and related health-care authorities and pharmaceutical companies. This study, however, was not supported by a pharmaceutical company. There were no other conflicts of interest to declare.

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All authors have approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2017.03.039>.

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