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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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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.

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 ±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 homoeostasis [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 (~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