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Gastrointestinal cancer incidence in type 2 diabetes mellitus; results from a large population-based cohort study in the UK

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ABSTRACT

Background: Patients with type 2 diabetes mellitus (T2DM) have been shown to have higher incidences of liver, pancreatic, and colorectal cancer compared to non-diabetic individuals. Current evidence is conflicting for other gastrointestinal (GI) cancers. Therefore, we aimed to determine incidence rates (IRs) of all GI cancers in patients with and without T2DM.

Methods: A cohort study was performed using the UK Clinical Practice Research Datalink (1988-2012). A cohort of antidiabetic drug users was matched at baseline to a non-diabetic cohort, by age, sex, and practice. Crude IRs and 95% confidence intervals (95% CI) of GI cancers per 100,000 person-years were calculated stratified by age, sex, and calendar year.

Results: 333,438 T2DM and 333,438 non-diabetic individuals were analyzed. IRs of liver (IR 26, 95% CI 24–28 vs. 8.9, 95% CI 7.7–10), pancreatic (IR 65, 95% CI 62–69 vs. 31, 95% CI 28–34), and colon cancer (IR 119, 95% CI 114–124 vs. 109, 95% CI 104–114) were significantly higher in the diabetic compared to the non-diabetic cohort, whereas the IR of oesophageal cancer was significantly lower (IR 41, 95% CI 39–44 vs. 47, 95% CI 44–51). Sex-specific IRs of colon cancer remained significantly higher in men with T2DM, and IRs of esophageal cancer remained significantly lower in women with T2DM.

Conclusion: In this study, T2DM patients were shown to have higher crude IRs of liver, pancreatic and colon cancer, but not of gastric, biliary, and rectal cancer. Moreover, the lower observed IRs of oesophageal cancer in diabetic patients warrants further investigation.

1. Introduction

There is a growing body of evidence on an increased risk of cancer in type 2 diabetic patients, including gastrointestinal (GI) malignancies [1–7]. However, the data are conflicting for specific GI cancer sites, such as the upper gastrointestinal tract and biliary system. The strongest associations have been found for liver and pancreatic cancer, although ascertainment bias and reverse causality may have played an important role [8–10]. Furthermore, age-sex stratified analyses have not always been reported, despite the demonstration of age- and sex-specific differences in cancer risk, with GI cancer occurring more frequently at a higher age and more frequently in men [1].

Type 2 diabetic patients may have an increased risk of GI cancers through several common risk factors, such an older age, exposure to alcohol, smoking, a high caloric diet, lack of physical activity, and increased body mass index (BMI) [1]. In addition, site-specific risk factors that are more prevalent among diabetic patients may play an important role. These include gastro-oesophageal reflux disease in oesophageal

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cancer, Helicobacter pylori infections in gastric cancer, gallstone formation in biliary tract cancer, and non-alcoholic fatty liver disease or cirrhosis in hepatocellular carcinoma [11–14].

The underlying biological mechanisms that may explain the association between type 2 diabetes mellitus and cancer have yet to be further unraveled. In general, three pathophysiological mechanisms have been proposed which act through metabolic, hormonal and inflammatory pathways, namely: hyperglycaemia/hyperinsulinaemia, insulin/insulin-like growth factor (IGF) axis and chronic inflammation. Hyperinsulinaemia stimulates IGF-1 production, which may subsequently promote tumor growth by induction of cell proliferation and inhibition of apoptosis. Hyperinsulinaemia is also the hallmark of insulin resistance, which in turn stimulates the release of pro-inflammatory cytokines causing a pro-inflammatory state [1].

Most studies have reported relative measures of risk of cancer with diabetes, without a focus on the absolute numbers regarding the incidence of GI cancer in the diabetic population. To our knowledge population-based incidence rates of all subtypes of GI cancers in diabetic patients versus matched controls are unknown. Therefore, our aim was to determine incidence rates of GI malignancies for each site of the digestive tract in type 2 diabetic and non-diabetic individuals in the United Kingdom (UK).

2. Materials and methods

2.1. Data source

Data were obtained from the UK Clinical Practice Research Datalink (CPRD). The CPRD is an ongoing primary care database that comprises anonymized electronic medical records from British general practitioners since 1987, with coverage of over 11.3 million patients from 674 practices [15,16]. Currently, the population of active patients represents 6.9% of the total UK population. CPRD records include demographic information, medication prescription details, clinical events, preventive care provided, diagnostic tests, specialist referrals, hospital admissions, and major outcomes [16]. The accuracy and completeness of CPRD data have been well-validated [17,18]. The protocol of this study was approved by CPRD's Independent Scientific Advisory Committee (Protocol 15_143).

2.2. Study population

To examine GI cancer incidence rates (IRs) across anatomic subsite, age, sex, and calendar year among type 2 diabetic patients and non-diabetic individuals, we included a cohort of antidiabetic drug (ADD) users (diabetic cohort) and a (1:1) matched reference cohort using incidence sampling technique (Supplementary Fig. S1). The diabetic cohort consisted of all registered adult patients (aged 18+ years) with at least one prescription for an ADD recorded in CPRD during valid data collection (January 1988-December 2012. The date of first ADD prescription defined start of follow-up (index date). Each diabetic patient was matched to a reference patient without any past recorded prescriptions for ADDs by sex, year of birth, and practice. Reference patients were assigned the same index date as their matched diabetic patient. Patients in the reference cohort could become diabetic patients if an ADD prescription was recorded. At the prescription date the patient was censored as a reference and matched, as a diabetic patient, to a new reference. Non-diabetic reference subjects could have suffered from any other disease than diabetes mellitus or those mentioned as exclusion criteria below.

Patients with a prescription for insulin at the index date, without a concomitant prescription for a non-insulin ADD, were excluded if (a) they had a recorded diagnosis for type 1 diabetes mellitus or (b) they were under 30 years of age at cohort entry. These patients were considered having type 1 diabetes mellitus. Secondly, all subjects with a history of the cancer of interest prior to cohort entry (i.e. all subjects with a history of gastric cancer when investigating gastric cancer) were excluded. Furthermore, all metformin only users who had a history of polycystic ovary syndrome (PCOS) prior to cohort entry were excluded, as they are more likely to receive metformin as a treatment for PCOS, instead of type 2 diabetes mellitus. In addition, we excluded diabetic patients without any subsequent prescriptions for an ADD (after the initial prescription recorded at baseline). All matched individuals of excluded subjects were excluded as well.

2.3. Outcome

All study participants were followed up from the index date to a diagnosis of a GI malignancy, the end of data collection, the date of transfer out of the practice area, or death, whichever came first. The first medical record for a GI cancer in CPRD after cohort entry was taken as the diagnosis date of a new case. Subsites of cancer were classified according to their anatomical location; i.e. cancer of the esophagus, stomach, liver, gallbladder and extrahepatic bile ducts (biliary), pancreas, small intestines, colon and rectum. A high level of validity for the recording of cancer in the CPRD has been previously reported [19].

2.4. Statistical analyses

To describe and compare both cohorts at baseline, we analyzed various lifestyle factors (smoking status, alcohol use, body mass index), a diagnosis of various comorbidities ever before (gallstone disease, gastro-esophageal reflux disease (GERD), Helicobacter pylori infection, hypertension, inflammatory bowel disease (IBD), chronic liver disease, and chronic pancreatitis), use of drugs during the past 6 months before start of follow-up (antihypertensives, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), proton-pump inhibitors, and statins), and if a subject had a colonoscopy for colorectal cancer screening purposes during the year before start of follow-up.

Overall, age-, sex-, and site-specific incidence rates (IR) per 100,000 person years (py) and incidence rate ratios (IRR) with 95% confidence intervals (CI) were calculated for GI cancers in the diabetic and reference cohort. IRRs were calculated by dividing the IR of the non-diabetic cohort by the IR of the type 2 diabetic cohort. Differences between IRs were tested for statistical significance using the normal-theory test ($\alpha < 0.05$) [20]. To assess secular trends, data were presented by age group and time period of cancer diagnosis. Age groups consisted of 5-year intervals, with the exception of those aged '18 through 29 years' (as cancer is rare these patients) and ending with '85+ years'. Calendar time was broken down into six periods: 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012. Time periods for 1988–2000 were not shown due to lower accuracy of CPRD database during that period. Due to a small number of small intestinal cancer cases, graphs for this cancer site are not shown as no reliable conclusions could be drawn. Furthermore, when the number of cases in a specific subgroup was less than six, data were not shown (suppressed) for reasons of patient privacy.

2.5. Sensitivity analyses

To prevent possible detection bias after the diagnosis of type 2 diabetes mellitus and account for possible reverse causality, a sensitivity analysis was performed by excluding the first year of follow-up after the index date from the analysis for all patients and subsequently calculating subsite- and sex-specific IRs during the remaining follow-up period. All data management and statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

During more than 3.6 million person-years of follow-up, 10,977 GI