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Impact of metformin on gastric adenocarcinoma survival: A Belgian population based study

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ABSTRACT

Background: Preclinical studies have shown anticancer activities of metformin in gastric cancer and a recent epidemiological study showed a decrease in recurrence and mortality of gastric cancer in metformin users. This study aimed to assess the impact of metformin on gastric cancer survival in diabetic patients at a Belgian population level.

Methods: We conducted an observational, population-based study by linking data of the Belgian Cancer Registry with medical claims data coming from the health insurance companies for patients diagnosed with stage I to III gastric adenocarcinoma between 2006 and 2012. Information on gastric cancer-specific deaths was retrieved from mortality records collected by regional governments. Time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for overall survival (OS) and cancer-specific mortality (CSS).

Results: In our population of 371 patients, a reduction in all-cause mortality was observed in metformin users (adjusted HR = 0.73, 95% CI: [0.52; 1.01], p = 0.06) but not for cancer specific mortality (adjusted HR = 0.86, 95% CI: [0.56; 1.33], p = 0.50). Pre-diagnosis exposure to metformin was associated with a significant improvement in OS (adjusted HR = 0.75, 95% CI: [0.57; 0.98], p = 0.04) that was not significant for CSS (adjusted HR = 0.89, 95% CI: [0.62; 1.28], p = 0.52). Moreover, no dose-response relationship between metformin use and either all-cause or cancer-specific mortality was observed.

Conclusion: In the first population based study of metformin use in gastric cancer adenocarcinoma patients with previous diabetes, our findings suggest that metformin use might improve overall mortality. However, no such association was found for cancer-specific survival. Additional studies in other populations are required.

1. Introduction

Gastric cancer is one of the most common cancers worldwide with more than 950 000 new cases diagnosed in 2012 [1]. Despite a recent decline in incidence in some European countries, gastric cancer remains one of the leading causes of cancer death globally, with approximatively 720 000 stomach cancer deaths in 2012 alone [1,2]. Similar to most European countries, in Belgium gastric cancer incidence is approximatively 5.4 per 100 000 men and 3.3 per 100 000 women and the five-year overall survival is approximatively 35% and 44% for men and women, respectively [3].

Diabetes and cancer have been studied intensely during the last decade and researchers focused on investigating the existence of a link between these two chronic conditions [4–6]. It has been shown that diabetes increases the risk of stomach, liver, pancreatic, colon, and rectum cancer [7,8]. Also, diabetes has been reported to be associated with premature death from several cancers [9].

Metformin is the most widely prescribed first-line treatment for type II diabetes and has a favourable safety profile, even in those without type II diabetes [10–13]. Experimental studies have shown that metformin can exert an anti-cancer effect on human cancer cells [14]. Evidence from observational and clinical studies, have shown

Abbreviations: BCR, Belgian cancer registry; IMA, intermutualistic agency; NNSS, national number for social security; ICD, international classification of disease; DDD, defined daily dose; OS, overall survival; CSS, cancer specific survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index

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metformin to be inversely associated with cancer risk and progression however results from individual studies have not been consistent [12,14–20].

For gastric cancer in particular, experimental studies demonstrate that metformin can inhibit human gastric cancer cell proliferation and metastasis and can inhibit tumour growth and enhance the effect of rapamycin and cisplatin in mouse models [21–24].

Randomized clinical trials are the gold standard for assessing treatment efficacy and safety. However, in the field of pharmacoepidemiology, such studies suffer from limitations compared to observational studies such as selection bias and short follow up durations [25]. Therefore, well conducted observational studies are a good alternative to confirm preclinical hypotheses.

To date, only one single-institution study in South Korea has investigated metformin use and mortality from gastric cancer and results were encouraging: a 14% decrease in recurrence and a 13% decrease in mortality risk for diabetic gastric cancer patients for each 6 month of cumulative use of metformin after gastrectomy [26].

Despite promising preclinical evidence, data on metformin use and gastric cancer mortality remain scarce and such pharmacoepidemiological studies haven't been conducted at a population level yet. Therefore, the current study aimed to examine the impact of metformin use on overall and cancer specific survival in 371 diabetic patients with gastric adenocarcinoma, at the Belgian population level. Based on previous evidence, we hypothesized that metformin use might increase survival in diabetic patients with gastric cancer.

2. Material and methods

2.1. Data sources

The Belgian Cancer Registry (BCR) is a population-based registry covering more than 95% of the Belgian population from 2004 onwards [3]. In addition to detailed patient and tumour characteristics collected through standard cancer registrations, the BCR has authorization to collect medical claims data from the health insurance companies. These data are gathered on a national level by the Intermutualistic Agency (IMA) and can be linked to the BCR data using the national number for social security (NNSS). Available IMA information covers all reimbursed diagnostic and therapeutic procedures and pharmaceuticals for in- as well as out-patient dispenses for a period ranging from one year before until five years after diagnosis for each cancer patient.

Vital status is also retrieved based on NNSS from the Belgian Crossroads bank for Social Security (BCSS). Causes of death are extracted from death certificate data collected by the regional governments and probabilistically linked to the BCR data (> 98% successfully linked).

Informed written consent was not needed for this study, because the use of BCR data for scientific purposes is regulated by Belgian law since 2006 [27].

2.2. Study subjects

All patients diagnosed between the 1st January 2006 and the 31st December 2012 with stage I–III gastric adenocarcinoma and previous diabetes were selected from the BCR database (International Classification of Diseases (ICD), 10th revision: C16.1–C16.9). Cancers of the gastro-oesophageal junction were excluded as they were considered to be oesophageal cancers.

In addition, patients who died in the first 6 months after diagnosis were excluded as drug use during this time is unlikely to exert an effect on cancer death.

A patient was defined to be diabetic if he had a record of anti-diabetic medications (ATC code "A10") dispensed with a total sum of > 30 daily defined doses (DDD) in the year prior to diagnosis.

Additional exclusion criteria were: presence of a previous tumour (apart from non-melanoma skin cancer), not residing in Belgium at the time of diagnosis, an uncertain date of diagnosis, no national number for social security (NNSS), lost to follow up at the date of cancer incidence, or missing from the medical claims (IMA) database.

Cardiovascular and respiratory comorbidities in the year prior to diagnosis were also derived from claims data including in-and outpatient dispensed medication, according to a previously described methodology [28]. A patient was defined to have cardiovascular or respiratory disease if cardiovascular medications (ATC code "C01–C04", "C07–C09" and "B01" with exclusion of heparin) or respiratory medications (ATC code "R03") with a total sum of > 180 DDDs and > 80 DDDs respectively were dispensed in the year prior to diagnosis.

2.3. Outcome

The primary outcome was overall survival and follow-up was until July 1st, 2015. In the cancer-specific survival analysis, patients were followed until January 1st, 2014. Patients who died after this date were censored. Cancer specific deaths were defined as those with an underlying cause of death coded with ICD-10 C16.1–C16.9 for gastric cancer or C26 for malignant neoplasm of other and ill-defined digestive organs.

2.4. Covariates

Information available from the BCR included data on cancer diagnosis and other demographic and clinical information: age in categories (< 70years, ≥70years), sex, year of diagnosis (from 2006 to 2012 recoded into a binary variable: 2006–2008 and 2009–2012), and combined stage (stage I–III).

Metformin use, as well as cancer treatments in the 6 months after diagnosis were derived from prescription records provided by the IMA. Cancer treatment categories included primary surgery, peri-operative treatment (chemotherapy, radiotherapy or both), primary chemotherapy and/or radiotherapy, and no treatment.

2.5. Statistical analysis

Users and non-users of metformin were compared using Pearson chi square test or Fisher exact test where the former was invalid.

For post-diagnosis metformin use, time-dependent cox regression models were used to calculate adjusted and unadjusted hazards ratios (HR) with 95% confidence intervals (CI). Patients became metformin users only after they were dispensed a metformin prescription, therefore avoiding immortal-time bias [29]. Before this prescription, patients were considered as non-users.

Drug use was lagged by 6 months after diagnosis to remove prescriptions occurring immediately prior to death as they may reflect palliative care. Sensitivity analyses were performed to study the effect of varying the length of this lag.

Dose response effects were explored in two types of time-varying analyses. Firstly, we investigated increasing number of prescriptions. A patient was classified a non-user if prior to the first metformin prescription. Light use was classified as use from the first prescription until the 6th prescription after diagnosis. A patient was considered a heavy user if he had the 6 or more metformin prescriptions after diagnosis.

Secondly, we investigated increasing number of defined daily doses (DDDs). In DDD analyses, patients were classified as non-users if they had less than 1 DDD after the diagnosis. Then, assuming that one DDD corresponds to one day of metformin use, we classified light users as 1–182.5 DDDs, and heavy users as more than 182.5 DDDs.

In secondary analysis, we investigated the association between prediagnosis metformin use in the year prior to diagnosis without excluding those with less than 6 months of follow-up after diagnosis.

In a simplified post-diagnosis use, we compared metformin users to non-users in the first six months after the cancer diagnosis in