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Metformin exposure and disseminated disease in patients with colorectal cancer

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ABSTRACT

Background: Preclinical evidence suggests a role for metformin in inhibiting tumour dissemination and metastasis. Previous studies have identified associations between metformin exposure and improved colorectal cancer survival. This study aimed to examine associations between metformin exposure and the odds of presenting with disseminated disease among colorectal cancer patients.
Methods: Colorectal cancer patients diagnosed 2001–2006 were identified from the National Cancer Registry Ireland. A linked national pharmacy claims database was used to determine exposure to anti-diabetic medications prior to diagnosis. Multivariate logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI) for associations between metformin use (versus non-metformin anti-diabetic drugs) and odds of presenting with disseminated disease (lymph node positive/metastatic). Analyses were stratified by anti-diabetic drug co-prescription and intensity of metformin exposure.
Results: The study population included 241 metformin-exposed diabetics, 129 non-metformin-exposed diabetics, and 4277 non-diabetic patients. In multivariate analysis, odds of disseminated disease were lower in metformin-exposed diabetics, compared with non-metformin-exposed diabetics, though not statistically significant (OR = 0.66, 95% CI 0.39–1.12). In analyses stratified by metformin dosing intensity and anti-diabetic drug co-prescription, the odds were further from unity and approached significance in diabetics with high intensity, exclusive metformin use (OR = 0.52, 95% CI 0.25–1.10).
Conclusions: While overall there was no statistically significant association between metformin exposure and disseminated colorectal cancer at diagnosis, there was a suggestion that high intensity, exclusive metformin use may be associated with reduced odds of disseminated disease. The number of patients in these subgroup analyses was small, and further investigation in larger studies is warranted.

1. Background

Among type II diabetic patients, exposure to metformin, versus other anti-diabetic treatments, has been associated with lower incidence of overall cancer and improved outcomes in patients with existing cancer [1]. Metformin has been linked in a number of studies to reduced incidence of colorectal cancer, in particular [2], and to improved colorectal cancer survival [3–5].

Recently a number of preclinical studies have also suggested that metformin may have a specific role in inhibiting tumour dissemination and metastasis [6–9]. Mechanisms proposed to explain a possible anti-metastatic effect of metformin include the suppression of metastasis-associated proteins [10,11], the inhibition of tumour stem cell function [12], and the reduction of angiogenesis via mTOR inhibition [13–15].

Tumour dissemination, and specifically the presence of lymph node and/or distant metastases, is one of the most important predictors of outcomes in colorectal cancer, determining both treatment decisions and prognosis [16]. In this study we sought to investigate, for the first time, associations between metformin exposure, versus other anti-diabetic drugs, prior to colorectal cancer diagnosis and the odds of presenting with disseminated disease (defined as lymph node positive disease or distant metastases at the time of diagnosis).

2. Patients and methods

2.1. Setting and data sources

The National Cancer Registry of Ireland (NCRI) provided all the data used in this study. The study dataset comprised anonymised individual-level patient records from the cancer registry which had previously been linked to pharmacy dispensing claims data from Ireland's Health Services Executive (HSE) – Primary Care Reimbursement Services (PCRS) database. The NCRI collects comprehensive information on all incident cancers in the population usually resident in Ireland. Registrations are identified from a range of data sources, including pathology and radiology reports,

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radiotherapy and chemotherapy records, and death certificates, by trained tumour registration officers. The HSE-PCRS General Medical Services (GMS) scheme provides taxpayer-funded free healthcare, including medicines, to approximately 38% (1.6 million) of the Irish population [17]. Eligibility for the GMS scheme for the period of the study was through means test in those under 70 years and universal for those aged 70 and older. The GMS pharmacy claims database contains detailed prescription information for all patients eligible for the scheme. The use for research of anonymised data held by the NCRI is covered by the Health (Provision of Information) Act 1997.

2.2. Study design

Patients over the age of 18 with AJCC stages I–IV invasive colorectal cancer (ICD-10 C18–C20) [18,19] diagnosed between 1st January 2001 and 31st December 2006 inclusive were eligible for inclusion in this retrospective observational study. Patients were also required to have no prior record of an invasive cancer other than non-melanoma skin cancer and to have eligibility for the GMS scheme for the year prior to colorectal cancer diagnosis. Patients were divided into two groups: 'diabetic' and 'non-diabetic'. Individuals were classed as diabetic if they were identified through the pharmacy claims data to have received a supply of at least one anti-diabetic drug (ADD; WHO ATC therapeutic subgroup A10 [20]) in the year prior to colorectal cancer diagnosis. All other patients were classified as non-diabetic.

2.3. Exposure definition

Metformin exposure was identified from the linked prescription refill data (Supplementary File 1); a patient was considered exposed (yes/no) if a supply of metformin was available to the patient at any point in the year prior to cancer diagnosis. Metformin dosing intensity was calculated as the proportion of days in the year prior to colorectal cancer diagnosis for which a supply of metformin was available [21]. This was stratified as 'low' or 'high' at the median. Exposure to sulfonylureas, insulin, and/or other ADDs (thiazolidinediones, DPP4 inhibitors, meglitinides and alpha glucosidase inhibitors) (yes/no; Supplementary File 1) was also identified.

2.4. Outcomes and comparisons

The study outcome was the presence of lymph node metastases and/or distant metastases at the time of cancer diagnosis (henceforth 'disseminated colorectal cancer'). Information on pathological and clinical assessment of nodal/distant metastatic involvement was taken from the NCRI database. Patients were classified as having 'disseminated colorectal cancer' (yes/no) if they had a nodal status of N1 or N2 at diagnosis or a metastatic status of M1. In these analyses, patients with unknown nodal status (11.6% in both metformin exposed and unexposed groups) were also classified as having 'disseminated colorectal cancer' as a conservative approach. Sensitivity analyses were later conducted around this assumption; patients with unknown lymph node status were classed as not having 'disseminated colorectal cancer', as described below under ''Sensitivity Analyses''.

The primary analyses were conducted within the diabetic subgroup; outcomes were compared between diabetics receiving metformin and a reference group comprising diabetics not receiving metformin. Secondary analyses were conducted such that diabetics receiving metformin were compared to non-diabetics. This was to address the concern that studies among diabetics may be biased due to differences in the severity of diabetes or the effectiveness of diabetes control between patients receiving metformin versus non-metformin ADDs [22,23].

2.5. Covariates

Patients' socio-demographic information and tumour details were abstracted from the NCRI database. Socio-demographic details included age at diagnosis, gender, smoking status at diagnosis (current, former, never, unspecified) and an indicator of socioeconomic status based on area of residence at diagnosis [24]. Tumour details included: AJCC summary stage, T-stage [18], tumour grade (well/moderately differentiated, poorly differentiated, unspecified), site (colon, rectum; Supplementary File 1), morphology (adenocarcinoma, other; Supplementary File 1), and year of diagnosis. Exposure to aspirin (yes/no; Supplementary File 1) was also considered due to recent evidence associating aspirin with reduced risk of metastases [25]. A comorbidity score was calculated for each patient based on the number of distinct drug classes (level 5 ATC codes) to which the patient was exposed in the year prior to diagnosis [26].

2.6. Statistical analysis

Patient characteristics were tabulated for diabetics, according to metformin exposure status (yes/no), and for non-diabetics; differences between the groups were explored using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test for categorical variables.

Within the diabetic subgroup, univariate and adjusted logistic regression models (SAS® PROC LOGISTIC) were used to estimate odds ratios (OR) with 95% confidence intervals (CI) for associations between metformin exposure (versus no metformin exposure) and disseminated colorectal cancer. Prior knowledge, literature review and causal diagrams were used to identify potential covariates for inclusion in the multivariate model [16,27,28]. The final multivariate model was then selected using backwards elimination based on a maximum cumulative change in the odds ratio of 10% [29,30]. Analyses were also conducted stratifying by (i) metformin dosing intensity and (ii) receipt of metformin exclusively or in combination with non-metformin ADDs and (iii) combinations of dosing intensity and metformin/non-metformin ADDs. Finally, analyses were repeated as above comparing metformin-exposed diabetics with non-diabetics. The confounder selection process for these analyses was carried out in the same manner as that for the primary analyses.

Analyses were performed using SAS®, version 9.2 (SAS® Institute Inc., Cary, NC). A two-sided P value of <0.05 was considered statistically significant.

2.7. Sensitivity analysis

As patients with unknown nodal status were coded as 'disseminated disease' in the primary analysis, analyses were carried out to test the sensitivity of this assumption. The outcome was reclassified such that only patients with known positive nodal status and/or known positive distant metastases were classed as having 'disseminated disease' and all analyses were repeated using this outcome definition.

3. Results

3.1. Patient characteristics

A flow chart illustrating patient selection criteria is presented in Fig. 1. Patient characteristics for metformin-exposed ($n = 241$) and unexposed ($n = 129$) diabetics, and non-diabetics ($n = 4277$), are