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Short communication

Metformin use and survival from lung cancer: A population-based cohort study

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ABSTRACT

Preclinical evidence suggests that metformin, a widely prescribed anti-diabetic drug, may inhibit lung cancer progression. We investigated whether metformin use was associated with decreased risk of cancer-specific mortality in lung cancer patients. This study included newly diagnosed lung cancer patients (identified from English National Cancer Data Repository, 1998–2009) with type 2 diabetes (based on UK Clinical Practice Research Datalink prescriptions and diagnosis records). Lung cancer deaths occurring up to 2012 were identified using Office of National Statistics mortality data and the association between metformin use (before and after diagnosis) and risk of lung cancer-specific mortality was calculated using Cox regression models. In analysis of 533 patients, we found a weak non-significant reduction in lung cancer-specific mortality with metformin use after diagnosis (adjusted HR, 0.86; 95% CI, 0.68–1.09). No association was evident for metformin use before diagnosis and cancer-specific mortality in analysis of 1350 patients (adjusted HR, 0.97; 95% CI, 0.86, 1.11). Associations were similar by duration of use. In addition, after adjustment for potential confounders, there was little evidence of an association between the use of other anti-diabetic medications (either before or after diagnosis) and lung cancer-specific mortality; including sulfonylureas, insulin or other anti-diabetic medications (such as thiazolidinediones). Overall, the results from this population-based study provide little evidence of a protective association between metformin use and cancer mortality in lung cancer patients.

1. Introduction

Emerging evidence from preclinical studies suggests a potential antitumour effect for metformin, a biguanide derivative commonly prescribed to treat type 2 diabetes, possibly due to the activation of AMP-activated protein kinase, leading to the inhibition of the mTOR signalling pathway [1]. Metformin use has been associated with improved survival in patients with diabetes with breast [2], colorectal [3] and prostate cancer [4]; however there are limited data in lung cancer patients. Constitutive mTOR signaling plays an important role in the development of lung cancer and *in vitro* and animal studies have reported antiproliferative effects [5] and proapoptotic effects [6], as well as the inhibition of lung tumour growth [7]. Few epidemiological studies have assessed the influence of metformin on lung cancer-specific outcomes after diagnosis. Some, but not all [8] have reported improvements in progression-free survival [9] and disease-free survival [10,11] but these investigations were limited by small sample sizes [8–11], drug exposure determined at limited numbers of time-points [8–11] and a lack of adjustment for important baseline patient characteristics [9]. Other studies have investigated metformin use and overall survival [12–14], but these results could reflect mortality from non-cancer causes.

In this population-based study, we investigate for the first time the impact of metformin use, either before or after diagnosis, on lung cancer-specific survival. Secondary analysis investigated the influence of other anti-diabetic medications.

2. Materials and methods

2.1. Study design

As described previously [15], we utilized record linkages between the English National Cancer Data Repository (NCDR)

Abbreviations: BMI, body mass index; CIs, confidence intervals; CPRD, Clinical Practice Research Datalink; DDD, daily defined dose; GP, general practitioner; HR, hazard ratio; NCDR, National Cancer Data Repository; ONS, Office of National Statistics; UK, United Kingdom; WHO, World Health Organisation.

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and the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) to identify lung cancer patients diagnosed between 1998 and 2009. Office of National Statistics (ONS) mortality data provided deaths up to 2012. We restricted the cohort to those with a prior diagnosis of type 2 diabetes (based on a GP diagnosis of diabetes or at least one anti-diabetic medication prescription). Patients with type 1 diabetes were excluded and were defined as those with a diagnosis of type 1 diabetes in addition to at least one prescription for insulin before their cancer diagnosis. Patients were also excluded if they had a previous cancer (with the exception of non-melanoma skin cancers) or if their diagnosis date preceded CPRD research quality records. Ethical approval for all observational studies conducted using CPRD data has been obtained from a multicentre research ethics committee.

2.2. Exposure data

Data on post-diagnostic anti-diabetic medication usage was determined from general practitioner (GP) prescribing records contained within the CPRD according to the British National Formulary (BNF) [16] including metformin, sulfonylureas, insulin or other anti-diabetic medications (including thiazolidinediones).

2.3. Covariates

The NCDR provided clinical data on tumour histology and receipt of cancer treatments including surgery, chemotherapy and radiotherapy. Information on lifestyle factors before diagnosis including smoking, alcohol and BMI was obtained from CPRD records. Comorbidities prior to diagnosis were derived from GP records and included those within a recent adaptation of the Charlson Comorbidity index [17]. A measure of deprivation was available from CPRD records [18]. Other medications including low-dose aspirin and statins were determined from GP-prescription records. Haemoglobin A1c (HbA1c) levels in the year prior to diagnosis were obtained from GP records.

2.4. Statistical analysis

2.4.1. Statistical analysis for anti-diabetic medication use after diagnosis

The analysis of drug use after diagnosis used Cox regression models to produce unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between anti-diabetic medication usage and lung cancer-specific mortality. Patients that died in the first 6 months after diagnosis were removed as drug use during this time is unlikely to exert an effect on cancer death. Therefore, follow-up time for all patients began from 6 months after lung cancer diagnosis. As outlined in Appendix A, Drug use was treated as time-varying [19], and was lagged by 6 months to remove prescriptions immediately prior to death (as these may reflect end-of-life care), an approach that has been used previously [20,21]. Dose-response relationships were investigated for metformin use by increasing number of prescriptions and defined daily doses (DDDs), as defined by the WHO [22]. Sub-group analyses for metformin use and lung cancer mortality were carried out by pre-diagnostic drug use and tumour histology. Separate sensitivity analyses additionally adjusted for smoking and HbA1c level (among individuals with available information) and type 2 diabetes duration (among individuals with at least 5 years of records before diagnosis).

2.4.2. Statistical analysis for anti-diabetic medication use before diagnosis

Cox regression models were utilised to calculate unadjusted and adjusted HRs and 95% CIs for the association between anti-diabetic medication usage in the year prior to diagnosis and lung cancer-specific mortality. Patients with less than 1 year of CPRD records prior to diagnosis were removed. Similarly, dose-response relationships for metformin use were examined. Sensitivity analyses additionally adjusted for smoking, HbA1c level and type 2 diabetes duration.

3. Results

3.1. Patient cohort

A total of 1443 lung cancer patients with diabetes were identified. The analysis of anti-diabetic medication use after diagnosis included 533 patients, after 910 patients with less than 6 months follow-up were excluded. The analysis of anti-diabetic medication use before diagnosis included 1350 patients, after 93 patients with less than 1 year of records prior to diagnosis were excluded. Patient characteristics by metformin use are listed in Table 1. Users were more likely to be diagnosed more recently, be younger, be obese, to have had surgery and chemotherapy and to be users of statins and other anti-diabetic medications (except insulin). Some comorbidities were less common in users of metformin after diagnosis, Table 1.

3.2. Association between anti-diabetic medication use after diagnosis and survival

The results for the association between anti-diabetic medication use after diagnosis and survival are presented in Table 2. Metformin use after diagnosis was weakly associated with a reduction in lung cancer death, however, after adjustment for potential confounders, results attenuated (adjusted HR 0.86, 95% CI 0.68–1.09) and there was no significant dose–response relationship by increasing number of prescriptions or DDDs. In sub-group analyses, results were similar after stratification by pre-diagnostic metformin use (non-users: adjusted HR 0.71, 95% CI 0.45–1.13; users: adjusted HR 0.83, 95% CI 0.41–1.69, p for interaction = 0.52) and tumour histology (small cell lung cancer: adjusted HR 0.61, 95% CI 0.23–1.60; non-small cell lung cancer: adjusted HR 0.85, 95% CI 0.63–1.14, p for interaction = 0.87). Additional adjustment for other factors did not materially alter effect estimates, including smoking (adjusted HR 0.86, 95% CI 0.68–1.10), HbA1c level (adjusted HR 0.88, 0.68–1.13) and diabetes duration (adjusted HR 0.82, 95% CI 0.62–1.10).

There was no evidence of an association for sulfonylurea or insulin use. There was a suggestion of an increased risk of cancer mortality with the use of other anti-diabetic medication (including thiazolidinediones); but analysis was not significant and based on only 45 users (adjusted HR 1.42, 95% CI 0.94–1.13).

3.3. Association between anti-diabetic medication use before diagnosis and survival

No association between metformin use prior to diagnosis and lung cancer-specific mortality was observed and no dose-response association was apparent, Table 2. The findings remained largely unchanged after additional adjustment for smoking, HbA1c level and type 2 diabetes duration (data not shown). Sulfonylurea, insulin and other anti-diabetic medication use were not associated with cancer-specific mortality, Table 2.

4. Discussion

Using population-based data, we observed a 14% non-significant reduction in cancer-specific mortality with metformin use after diagnosis in a large cohort of lung cancer patients with pre-existing