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Association of dipeptidyl peptidase 4 inhibitors with risk of metastases in patients with type 2 diabetes and breast, prostate or digestive system cancer

Wolfgang Rathmann [a], Karel Kostev [b,*]

[a] Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University, Düsseldorf, Germany
[b] Epidemiology, QuintilesIMS, Frankfurt, Germany

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ABSTRACT

Aims: Experimental and animal studies have supported the hypothesis that dipeptidyl peptidase-4 inhibitors (DPP-4i) may accelerate tumor metastasis. The aim was to analyze the relationships between DPP-4i therapy with risk of metastases in type 2 diabetes patients with breast, prostate and digestive organ cancers.
Methods: Type 2 diabetes patients with first diagnoses of breast, prostate or digestive organ cancer were selected in general and internal medicine practices (Disease Analyzer Germany: 01/2008–12/2014). Propensity score matching between DPP-4i users and non-users was carried out for age, sex, diabetes duration, and metformin use. Time-dependent Cox regression models were used to estimate hazard ratios (HR) for metastases further adjusting for HbA1c, body mass index, comorbidity and co-therapy with glucose-lowering drugs (3–4 years follow-up).
Results: 668 patients with newly diagnosed breast cancer, 906 with prostate cancer and 908 with digestive organ cancer were analyzed. In Cox regression, use of DPP-4i was not associated with an increased risk of metastases in patients with breast (adjusted HR, 95%CI: 1.00, 0.49–2.02), prostate (0.98, 0.54–1.77) or digestive organ cancers (0.97, 0.57–1.66).
Conclusions: This first observational study in patients with type 2 diabetes and breast, prostate or digestive organ cancer found no increased risk of metastases in DPP-4i users.

1. Introduction

Epidemiological studies indicate an increased risk of liver, pancreas, breast, colorectal, urinary tract, and female reproductive organ cancers in type 2 diabetes patients and a reduced incidence of prostate cancer in men with diabetes (Giovannucci et al., 2010; Vigneri, Frasca, Sciacca, Pandini, & Vigneri, 2009). The link between type 2 diabetes and cancer has been related to shared underlying risk factors (e.g. obesity, physical inactivity, smoking), direct effects of metabolic alterations in patients with diabetes (e.g. hyperinsulinemia and the insulin-like growth factor-1 axis), or as side effects of glucose-lowering drug therapy (Giovannucci et al., 2010; Walker, Johnson, & Wild, 2013).

Little is known on the relationships of glucose-lowering drugs with tumor progression in type 2 diabetes patients (Jacob, Kostev, Rathmann, & Kalder, 2016). A reduced incidence of metastases associated with metformin therapy in women with breast cancer and type 2 diabetes was reported in a retrospective general practice study (Jacob et al., 2016). Furthermore, a clinic-based observational study found that breast cancer patients with diabetes who did not take metformin and patients without diabetes tended to have a higher risk of distant metastases (Bayraktar et al., 2012).

The relationships of other glucose-lowering drugs than metformin with cancer risk have rarely been studied. A known substrate of DPP4i is a stromal derived factor-1 (SDF-1), that could play a role in explaining the possible relationship between DPP-4i treatment and cancer. Recently, the effects of dipeptidyl peptidase-4 inhibitors (DPP-4i) on proliferation and migration of cancer cells have been investigated in experimental and animal studies (Wang et al., 2016). Both saxagliptin and sitaglitpin increased cell migration and invasion of colon, hepatic, breast, lung, ovary, and melanoma cancer cell lines (Wang et al., 2016). Furthermore, saxagliptin and sitagliptin treated mice developed more metastatic nodules in livers and lungs in an experimental metastatic model (Wang et al., 2016). Therefore, the aim was to analyze the relationships between DPP-4i therapy with risk of metastases in type 2 diabetes patients with breast, prostate and digestive organ cancers.

* Corresponding author at: Epidemiology, QuintilesIMS, Darmstädter Landstraße 108, 60598 Frankfurt am Main. Tel.: +49 69 66 04 4878.
E-mail address: kkostev@de.imshealth.com (K. Kostev).

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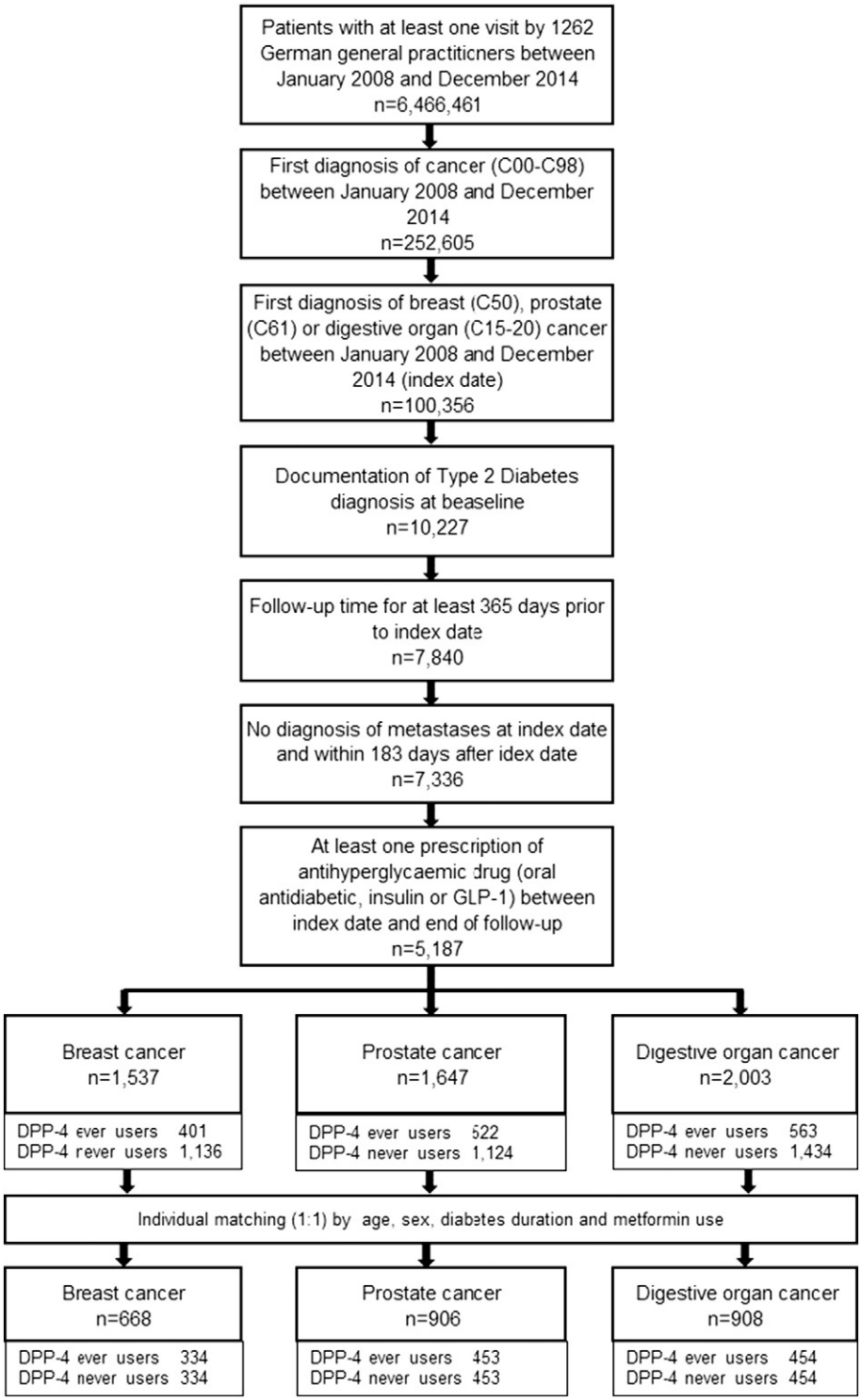

Fig. 1. Flow chart of patients with cancer and type 2 diabetes (Disease Analyzer database).

2. Subjects, materials and methods

2.1. Study design, setting and source data

In this retrospective observational study data were extracted from the Disease Analyzer database (Becher, Kostev, & Schröder-Bernhardi, 2009; Kowall, Rathmann, & Kostev, 2015). Disease Analyzer contains anonymized longitudinal data on drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the computer system of a representative sample of general practitioners and internal medicine practices throughout Germany.

The analyzed database period for the current study was January 1, 2008 to December 31, 2014 (1154 general and internal medicine practices). Patients with first ICD-10 diagnoses of breast (C50), prostate (C61) or digestive organ (C15-C20) cancer during the study period (index date, ID) were selected. The practice visit records were used to assemble baseline data 365–0 days before ID. Patient were included in the study if they: (1) had ≥1 documented type 2 diabetes

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