Journal of Diabetes and Its Complications xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

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

ARTICLE INFO

Article history:
Received 17 December 2016
Received in revised form 20 January 2017
Accepted 22 January 2017
Available online xxxx

Keywords:
Type 2 diabetes
Dipeptidyl peptidase 4 inhibitors
Breast cancer
Prostate cancer
Digestive system cancer

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).

http://dx.doi.org/10.1016/j.jdiacomp.2017.01.012
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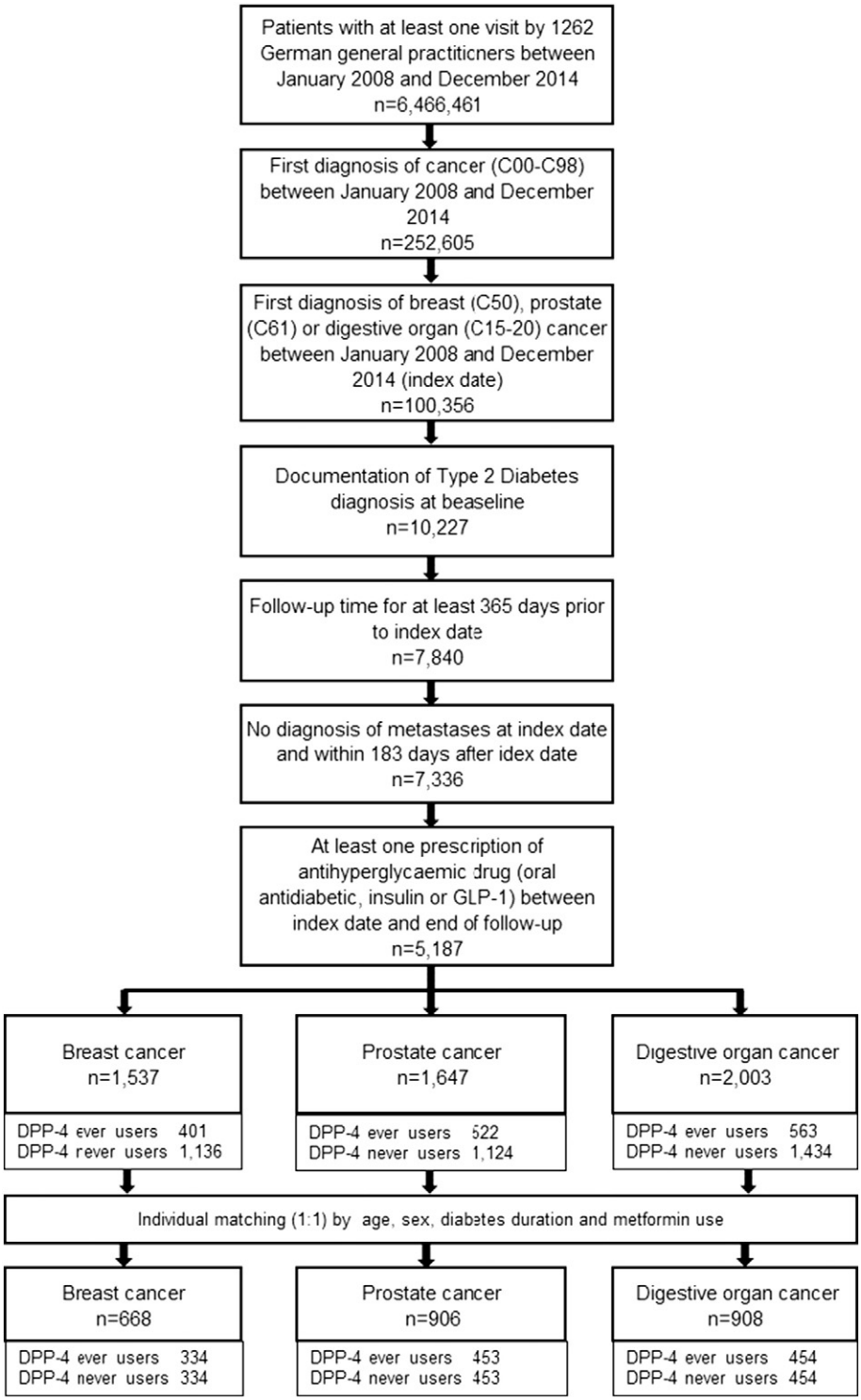

Fig. 1. Flow chart of patients with cancer and type 2 diabetes (Disease Analyzer database).

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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Table 1
Characteristics of type 2 diabetes with breast, prostate or digestive organ cancer diagnoses treated in primary care practices with and without DPP-4 inhibitor (DPP-4i) prescriptions after propensity score matching.

	Breast cancer		Prostate cancer		Digestive organ cancer	
Variables	DPP-4i (yes)	DPP-4i (no)	DPP-4i (yes)	DPP-4i (no)	DPP-4i (yes)	DPP-4i (no)
N	334	334	453	453	454	454
Age (years)	70.3 (9.3)	70.3 (9.3)	72.0 (6.9)	72.0 (6.9)	72.4 (8.0)	72.4 (8.0)
Diabetes duration (years)	4.9 (3.6)	4.9 (3.6)	4.7 (3.4)	4.7 (3.4)	5.0 (3.3)	5.0 (3.3)
Men	0.6	0.6	100	100	63.9	63.9
Diabetologist care	7.2	9.3	11.7	10.4	10.6	10.2
Private health insurance	6.3	3.6	12.4	9.1	9.3	7.1
Baseline diagnoses (%):						
Hyperlipidemia	54.2	57.2	58.3	54.1	61.2	54.9
Hypertension	84.1	84.1	81.5	82.1	82.8	83.7
Macrovascular complications	34.7	36.2	47.5	47.0	49.1	49.1
Microvascular complications	28.6	28.7	31.6	32.2	37.4	37.7
HbA1c (%)	7.3 (1.0)*	7.0 (1.0)*	7.3 (1.0)*	7.0 (1.0)*	7.2 (1.0)*	7.0 (1.0)*
Body mass index kg/m^2	31.9 (6.1)	31.5 (5.6)	30.3 (5.0)	29.3 (4.7)	29.1 (5.0)	29.6 (5.3)
Comedication (%):						
Metformin	78.4	78.4	80.4	80.4	74.0	74.0
Sulfonylureas	27.8*	16.2*	28.9	26.3	23.8	25.1
Insulin	35.0	36.2	35.5	33.8	37.9	39.9
GLP-1 receptor agonists	3.0	1.8	4.4*	1.8*	3.1	1.5
SGLT-2 inhibitors	7.8*	1.2*	6.8*	1.3*	3.5	1.8
Other glucose-lowering agents	11.1*	6.3*	10.4	7.7	11.0	7.5

Data are mean (SD) or percentage (%).
Macrovascular: myocardial infarction, coronary heart disease, stroke; microvascular: retinopathy, neprophathy, neuropathy.
*p-values <0.05 (paired t-tests, McNemars tests).
Other glucose-lowering agents: glinides or alpha-glucosidase inhibitors.
To convert HbA1c from percentage to mmol/mol, multiply by 10·93 and subtract 23·50.

diagnosis (E11) 365–0 days before ID, (2) had no documentation of cancer metastases 0–183 days after ID to exclude those with cancer metastases at baseline and (3) had at least one prescription of glucose-lowering drugs (oral antidiabetic agents, insulin, GLP-1 glucagon-like peptide-1 receptor (GLP-1) agonists) between ID and end of follow-up to exclude patients on dietary treatment only. During the study period, the following DPP-4i were used: sitagliptine, vildagliptine, saxagliptine.

2.2. Data analysis

Baseline data included patient age, sex, type of health insurance (private or statutory), diabetologist care, body mass index, HbA1c, macrovascular (myocardial infarction, coronary heart disease, stroke) and microvacular (retinopathy, nephropathy, neuropathy) complications. Furthermore, co-medication with glucose-lowering drugs, and prevalence of lipid disorders and hypertension were assessed.

To control for confounding, one-to-one matching was carried out based on a propensity score that was constructed as the conditional probability of DPP-4i use as a function of age, sex, diabetes duration and baseline metformin treatment (logistic regression). First DPP-4i treated patients were selected at random. Greedy matching was used by choosing an untreated patient whose propensity score was closest to that of this randomly selected treated subject for matching.

Descriptive statistics were given and group differences (DPP-4i users vs. non-users) were assessed using paired *t*-tests or McNemars tests after propensity score matching. The main analyses were performed separately for breast, prostate and digestive organ cancer patients. The outcome of interest was the time from the first cancer diagnosis up to first metastasis diagnosis or the end of the study period (31 December 2014), whichever came first. The analyses of metastases-free survival were carried out using Kaplan–Meier curves and stratified log-rank tests. A multivariate Cox regression model was fitted with incident metastases as dependent variable. Baseline HbA1c, body mass index, diabetologist care, private health insurance, comorbidity (hypertension, lipid disorders, macro- and microvascular complications) and co-therapy (sulfonylureas, insulin, other glucose-lowering drugs) were included as independent variables. A time dependent exposure definition was used: each patient-day was

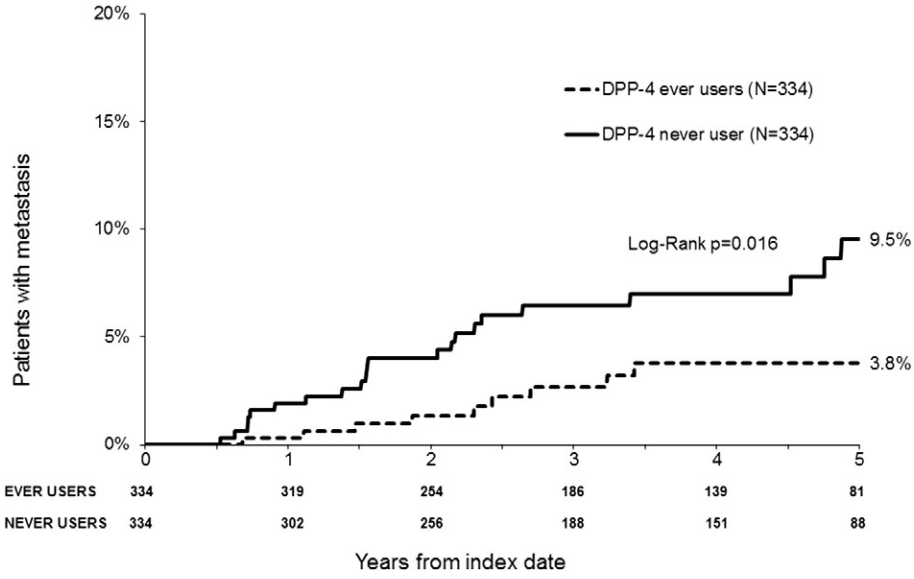

Fig. 2. Kaplan–Meier curves for time to incident metastasis diagnosis in primary care type 2 diabetes patients newly diagnosed with breast cancer as a function of DPP-4 inhibitor therapy.

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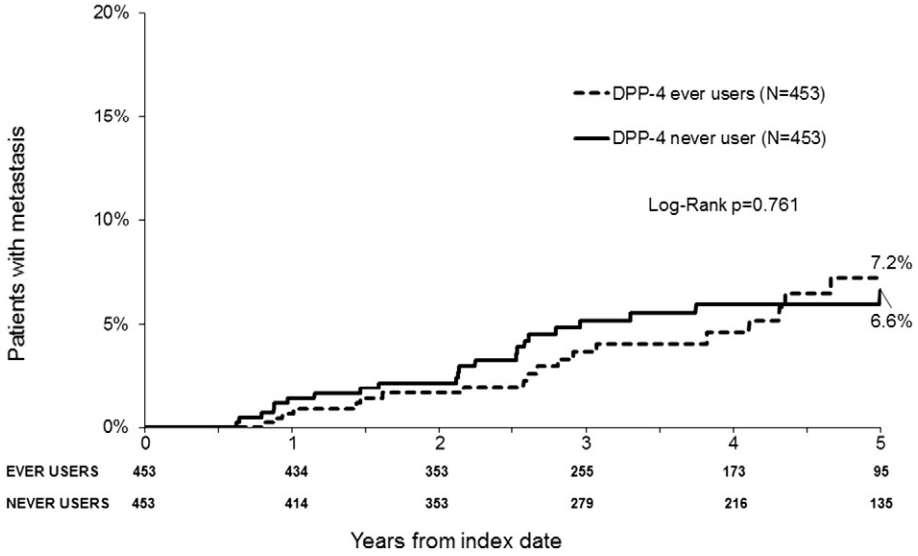

Fig. 3. Kaplan–Meier curves for time to incident metastasis diagnosis in primary care type 2 diabetes patients newly diagnosed with prostate cancer as a function of DPP-4 inhibitor therapy.

classified into one of two categories (DPP-4i exposition: yes/no). DPP-4i exposure time (days) was calculated based on prescribed daily dosages and package sizes. Time-dependent hazard ratios (HRs) and 95% CIs were estimated from Cox regression models accounting for clustering (Allison, 2010). Patients were censored at their last practice visit. P-value of <0.05 was considered as statistically significant. All analyses were carried out following the German good practice recommendations of secondary data analysis (Swart et al., 2015) using SAS 9.4 (SAS Institute, Cary, USA).

3. Results

After propensity score matching (1:1), 668 patients with breast cancer, 906 with prostate cancer and 908 with digestive organ cancer were analyzed, of whom half were treated with DPP-4i (Fig. 1). The baseline characteristics of DPP-4i users and non-users are shown in Table 1. After matching, the baseline characteristics for age, sex, diabetes duration and metformin prescriptions were similar for both cohorts (DPP-4i: yes/no) in all three cancer groups. Prevalence of macro- and microvascular complications were also not different, as well as frequency of hypertension and hyperlipidemia. The mean recorded body mass index was also similar in DPP-4i users and non-users at baseline. Finally, the prevalence of patients who were in diabetologist care and the frequency of privately insured patients as a crude proxy of socioeconomic status were not significantly different.

In all cancer groups, patients initiating DPP-4i treatment had higher baseline HbA1c values ($p < 0.05$). In breast cancer patients, DPP-4i users received more often sulfonylurea, SGLT-2 inhibitor and other glucose-lowering drug (glinides, alpha-glucosidase inhibitors) prescriptions at baseline. In prostate cancer patients, GLP-1 receptor agonists and SGLT-2 inhibitors were also more often prescribed in DPP-4i users. No differences in glucose-lowering drug prescriptions were found in digestive organ cancer patients for the two cohorts (DPP-4i: yes/no).

The average follow-up durations (mean, SD) were comparable for both groups (DPP-4i users vs. non-users: breast cancer: 3.6 (2.9) vs

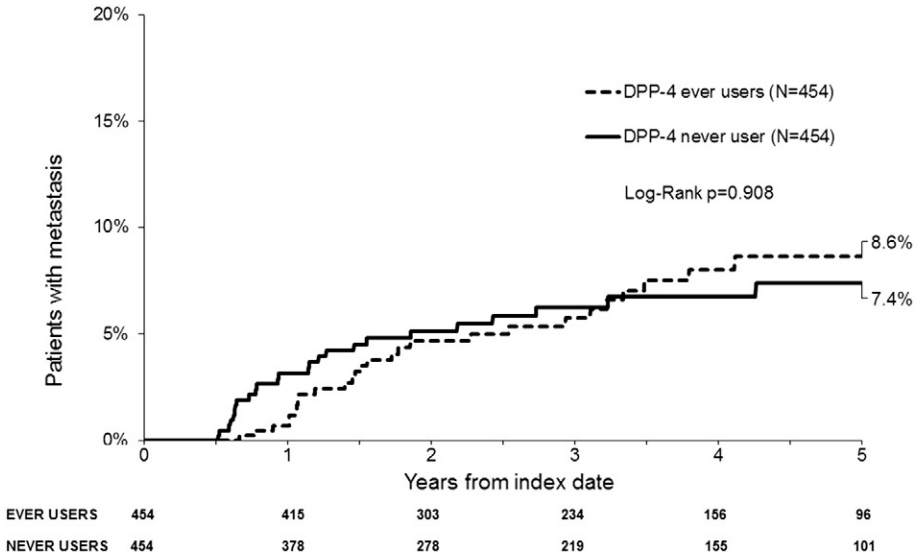

Fig. 4. Kaplan–Meier curves for time to incident metastasis diagnosis in primary care type 2 diabetes patients newly diagnosed with digestive organ cancers as a function of DPP-4 inhibitor therapy.

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Table 2
Association of DPP-4 inhibitor (DPP-4i) therapy with risk of metastases in primary care patients with breast, prostate and digestive organ cancer and type 2 diabetes: time dependent Cox regression analyses.

	Breast cancer	Prostate cancer	Digestive organ cancer
Model 1: DPP-4i prescriptions	0.69 (0.27–1.76)	0.99 (0.49–1.99)	1.37 (0.80–2.36)
Model 2: DPP-4i prescriptions	1.00 (0.49–2.02)	0.98 (0.54–1.77)	0.97 (0.57–1.66)

Data are time dependent hazard ratios (95% confidence intervals).
Model 1: adjusted for age, sex, diabetes duration and metformin use (matching).
Model 2: adjusted for baseline HbA1c, baseline body mass index, diabetologist care, private health insurance, hyperlipidemia, hypertension, macro- and microvascular complications, glucose-lowering therapy: sulfonylureas, GLP-1 receptor agonists, SGLT-2 inhibitors, insulin, other agents.

3.7 (2.9) years, $p = 0.643$; prostate cancer: 3.4 (2.6) vs 4.0 (3.0) years, $p < 0.001$; digestive organ cancer: 3.2 (3.1) vs 3.0 (3.4) years, $p = 0.426$). In breast cancer patients, the cumulative incidence of metastases was 3.8% for the DPP-4i users and 9.5% for the patients without DPP-4i over the study period of 5 years (Fig. 2). The DPP-4i users were at a decreased risk of metastases, which started already during the first year after index date and persisted over the whole study period. The metastases-free survival curves showed a difference between the two groups ($p = 0.016$). In prostate cancer (Fig. 3) and in digestive organ cancers (Fig. 4), there were no differences between DPP-4i users and non-users in the Kaplan–Meier curves.

In time dependent Cox regression models, use of DPP-4i was not associated with an increased risk of metastases in type 2 diabetes patients with breast, prostate or digestive organ cancers (Table 2). After further adjusting for baseline HbA1c, body mass index, diabetologist care, private health insurance, co-morbidity and co-medication with other glucose-lowering drugs similar hazard ratios were found in the three cancer cohorts, which were all close to the null.

4. Discussion

To our knowledge, this is first observational study which investigated the relationships between prescription use of DPP-4i and risk of metastases in type 2 diabetes patients with breast, prostate, or digestive organ cancers. DPP-4i were not associated with a higher risk of metastases within three to four years after cancer diagnoses.

Recently, experimental and animal studies have supported the hypothesis that DPP-4i may accelerate tumor metastasis (Wang et al., 2016). The results indicated that saxagliption and sitagliptin enhance the invasive capacity of various cancer cells, which promoted tumor metastasis. Both DPP-4i activated nuclear factor E2-related factor 2 (NRF2). NRF2 activation has been shown to increase the ability of cancer cells to migrate resulting in higher risk of metastases (Wang et al., 2016).

Understanding the effects of glucose-lowering drugs on tumor biology is important because of the increased cancer risk of patients with type 2 diabetes (Giovannucci et al., 2010; Vigneri et al., 2009). Dipetidyl peptidase 4 (DPP-4) is an aminopeptidase, which is present on epithelial cells in various organs (Choi et al., 2015). DPP-4 regulates the activities of peptide factors, which control signal transduction in a number of key cellular systems including several cytokines and chemokines (Choi et al., 2015). DPP4 has been shown to affect the invasive activity of cells on which it is expressed (Havre et al., 2008). Therefore, DPP 4 was suggested to act as a regulatory protein in cancer progression (Varona et al., 2010). In line with these finding, soluble DPP4 activity correlated with the aggressiveness of tumors (renal cell carcinoma) (Varona et al., 2010).

DPP-4i has been developed to inhibit the degradation of glucagon-like peptide-1 (GLP-1) (Drucker & Nauck, 2006). GLP-1 is a gut-derived incretin hormone, which stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite. Experimental and animal studies indicated that GLP-1 receptor signaling could influence intestinal tumorigenesis (Koehler et al., 2015). It is noteworthy that after bariatric surgery, which leads to higher levels of GLP-1, an increased risk of colorectal cancer has been reported (Derogar et al., 2013). Thus, existing results from experimental studies are compatible with a tumor promoting effect of incretin-based drugs.

So far, results from randomized controlled trials whether DPP-4i may promote specific types of cancer or may increase cancer risk in general are inconclusive (Nauck & Friedrich, 2013). The conduct of further studies on cancer risk in DPP-4i is important, because these drugs are increasingly used as second or third line drugs in treatment of type 2 diabetes (Inzucchi et al., 2015). Because of their efficacy in reducing HbA1c without side effects like hypoglycemia and weight increase it has been even stated that DPP-4i should be used earlier after type 2 diabetes diagnosis (Wilding, Rajeev, & DeFronzo, 2016). On the other hand, there has been a major debate in the past years on the safety of the use of incretins, particularly with regard to cancer (Butler, Elashoff, Elashoff, & Gale, 2013; Tseng, Lee, & Tseng, 2015; Azoulay et al., 2016). Therefore, further observational studies are required to exclude an increased risk of metastases with use of DPP-4i in patients with type 2 diabetes and cancer.

Because the present study used primary care records, a number of limitations should be mentioned. First, assessment of cancer and co-morbidities relied on ICD codes filled in by primary care physicians only. In addition, cancer stage was not documented in the database. Furthermore, the metastatic potential of digestive organ cancers may vary which could not be investigated due to the limited number of cancer cases. Finally, measurements of HbA1c and body mass index values were not standardized. The strength of the study is the large nationwide database and the unbiased assessment of prescriptions and outcomes (no recall bias). Second, we used a time dependent definition of DPP-4i exposure. Finally, important confounders were taken into consideration by propensity-score based matching of cohorts and additional adjustment using regression models. Nevertheless, residual confounding from unmeasured (e.g. lifestyle factors: physical activity, smoking) or unknown variables (e.g. cancer family history) is possible. Misclassification of the outcome (metastases) is also possible, however, most likely resulting in non-differential misclassification. Moreover, the database does not contain the data of oncologists or hospital data. Finally, the number of patients on DPP4i was limited. Thus, the results should be interpreted with caution.

4.1. Conclusion

In conclusion, this first observational study in primary care patients with type 2 diabetes and breast, prostate or digestive organ cancer found no increased risk of metastases in DPP-4i users. Although these results provide some assurance to patients and physicians, further studies including larger samples and longer follow-up are required to confirm the safety of DPP-4i in patients with comorbidity of type 2 diabetes and cancer.

Acknowledgements and funding

The study was funded by an unrestricted grant from QuintilesIMS.

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