Use of statins offsets insulin-related cancer risk

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Aim. There is firm evidence of a relation between type 2 diabetes (T2DM) and increased risks of cancer at various sites, but it is still unclear how different antihyperglycaemic therapies modify site-specific cancer risks. The aim of this study was to provide a complete characterization of all possible associations between individual T2DM therapies, statin use and site-specific cancers in the Austrian population.

Methods. Medical claims data of 1,847,051 patients with hospital stays during 2006–2007 were used to estimate age- and sex-dependent co-occurrences of site-specific cancer diagnoses and treatment with specific glucose-lowering drugs and statins.

Results. Patients treated with insulin or insulin secretagogues showed up to ninefold increased risks for cancers of the colon [males only (m)], liver (m), pancreas, lung (m) and brain (m), as well as a strongly decreased risk for prostate cancer (m). In patients taking statins, the risks were generally decreased, with a greater risk reduction in patients not receiving antihyperglycaemic therapies. The strongest effects were observed for use of insulin and pancreatic cancer [m: OR 4.5, 95% CI: 3.1–6.6; females (f): OR 4.2, 95% CI: 2.5–7.1], sulfonylureas (m: OR 2.8, 95% CI: 1.7–4.6; f: OR 3.0, 95% CI: 2.1–4.2) or glitazones and skin cancer (f: OR 0.54, 95% CI: 0.36–0.80), as well as metformin and cancer of the prostate (m: OR 0.82, 95% CI: 0.75–0.91) and corpus uteri (f: OR 1.7, 95% CI: 1.4–2.0) and non-Hodgkin’s lymphoma (f: OR 0.76, 95% CI: 0.64–0.91).

Conclusions. The use of statins offsets insulin-related cancer risks in patients with diabetes independently of sex and age. Overall, our data support the hyperglycaemia–cancer hypothesis. A reduction in endogenous or exogenous hyperinsulinaemia may be beneficial for cancer prevention. Therefore, insulin-sparing and insulin-sensitizing drugs should be the preferred treatment choices.

Keywords: epidemiology, insulin therapy, medical claims data, oral antihyperglycaemic agents, site-specific cancer risks, statin therapy.

Introduction

Although a large body of evidence indicates a higher risk of site-specific cancers in diabetic subjects, data are still controversial and the pathophysiological mechanisms are still not completely understood [1–3]. A central puzzle is that despite the firm evidence of a relation between type 2 diabetes (T2DM) and increased risk of cancer, it has been shown that improving glycaemic control in T2DM does not reduce cancer risk [4, 5]. This might be explained by the fact that different antihyperglycaemic medications modify cancer risk in different ways [6, 7]. It has been argued that administering exogenous insulin (acting as a growth factor) could also stimulate neoplastic growth [8]. Decreased cancer risk with use of metformin has been reported [9], whereas sulfonylureas might be associated with increased cancer risk [10, 11], and results for thiazolidinediones are inconclusive with a tendency towards a modestly decreased risk [12]. A more detailed understanding of these relationships is complicated by several factors. First, many of these studies lack patient samples of sufficient size to investigate the influence of the site of the cancer [7]. Secondly, there is a confounding influence of several shared risk factors of diabetes and cancer, and thirdly, antihyperglycaemic therapies depend on the sex and age of patients. Diabetes and increased BMI are risk factors for different cancers [13, 14] and are associated with increased cancer mortality, both in a site- and sex-specific manner [15, 16].
To address these shortcomings, we investigated the associations between site-specific cancers and antihyperglycaemic therapies using medical claims data from all hospitalized patients in the Austrian population. Our aim was to clarify the relationships between prevalence of specific cancers and T2DM as well as antihyperglycaemic and antihyperlipidemic treatment using two independent statistical approaches. The large sample size implies that age- and sex-dependent as well as site-specific results can be obtained for a particular drug whilst controlling for the influence of all other antihyperglycaemic drugs. Additionally, we were able to control for the presence of other treatments that might modify cancer risk, in particular statin therapy [17]. Statin therapy is common in diabetic subjects according to national and international guidelines of targeting less than 100 mg dL\(^{-1}\) Low Density Lipoprotein (LDL) cholesterol or in the presence of cardiovascular disease even less than 70 mg dL\(^{-1}\).

From a methodological point of view, one of the main novelties of our study was a data-driven approach in which we simultaneously tested all possible measurable relations between site-specific cancer risks and both antihyperglycaemic and antihyperlipidemic treatments in a nationwide data set of inpatients and retrieved only those results that showed the strongest statistical significance. As correlation does not imply causation, it is important that our results should be interpreted in the sense that patients with a particular treatment are more or less likely to require cancer-related inpatient care.

**Study design and methods**

**Patient data**

Our patient cohort consisted of all patients who received inpatient treatment in Austria during the years 2006 and 2007; patients who were born or died in these years were excluded [18, 19]. Patients with a diagnosis of type 1 diabetes were also excluded to eliminate the effects of absolute insulin deficiency and autoimmune disease and to obtain a more homogenous group of patients with T2DM and a wide range of possible glucose-lowering medications. The sample consisted of 1 847 051 patients (1 057 307 women and 789 744 men). For these patients, we extracted International Classification of Diseases, 10th revision (ICD10) codes of their diagnoses (main and secondary diagnoses) and Anatomical Therapeutic Chemical (ATC) Classification System codes of their medications.

Patients with malignant neoplasms were identified as those with a diagnosis with an ICD10 code starting with the letter ‘C’.

**Statistical analysis**

We performed two different statistical evaluations of the relations between site-specific cancer risks, antihyperglycaemic drugs and statin use. First, we grouped the patients according to whether they were prescribed statins or certain glucose-lowering drugs, and computed site-specific cancer risks within these groups. We refer to this analysis as ‘co-occurrence analysis’. Patients were divided into five groups based on their medications as shown in Fig. 1. Group 1 consisted of patients with a prescription for glucose-lowering drugs (ATC code starting with ‘A10’). Group 2 included patients treated with an insulin-sparing medication (metformin, glitazones and alpha-glucosidase inhibitors) and no insulin-providing medications or statins. Group 3 comprised patients treated with insulin-providing medications (insulin, sulfonylureas and glinides) and no insulin-sparing drugs or statins. Group 4 included patients treated with statins but no glucose-lowering drugs. Group 5 contained patients treated with statins and glucose-lowering drugs. Each group was compared to a control group of patients not treated with statins or glucose-lowering drugs if there were at least five cases for the given age group and cancer site. The age- and sex-dependent odds ratios (ORs) between 88 site-specific cancer risks and diabetes medications were computed. The false discovery rate was controlled using the linear step-up Benjamini–Hochberg multiple hypothesis test. This procedure is applicable for independent and several common correlated test statistics that include certain types of positive regression dependence and negative correlations in two-sided tests of normally distributed statistics [20, 21].

In the second analysis, we assigned all patients a set of binary variables, one for each medication, encoding whether or not they were prescribed the given medication. We computed the site-specific cancer risks for each combination of drugs and performed multiple logistic regressions of the observed cancer risks in the presence of specific drugs. Each patient was described by 16 binary variables corresponding to the 16 groups of medications (10 groups for diabetes medications corresponding to the five-digit ATC codes and six groups for different types of statins). The variable
was one if a patient was prescribed the drug, and zero otherwise. Of the 216 unique possible combinations of the 16 drugs, 2208 actually occurred. The observations were weighted by their number of patients. If there were fewer than 20 patients, the weight was set to zero. This reduced the set of different medications in the analysis from 2208 to 310, for which we computed the cancer risks for cancer sites with at least 1000 patients. The composite cancer risk for each combination of drugs was computed as the relative number of patients with at least one cancer diagnosis. To control for age dependence, we included only patients above 50 years of age and used the average age of patients in each group of medications as a measurement variable.

The co-occurrence analysis allowed us to directly measure correlations between site-specific cancer risks and the most common combinations of drugs, whereas the regression analysis allowed us to investigate the influence of individual drugs on cancer risks in an indirect way. In addition, the co-occurrence analysis allows in principle for all possible interactions between the drugs in a particular group, whereas the regression analysis assumes that no such interactions are relevant.

Results

Co-occurrence analysis

Results for the age-dependent ORs in each of the five groups are shown in Fig. 2. Only sites with at least one significant result are shown, and the ORs were set to one if they failed to be significantly different from one. A false discovery rate of \( \alpha = 0.2 \) was used for the linear step-up Benjamini–Hochberg multiple testing correction, which corresponds to an adjusted \( P \)-value of <0.036 when averaged over all groups and ages. The corresponding ORs and their 95% CIs are also shown in Figures S1 and S2.

There was a tendency towards decreased composite cancer risks in group 1 (all patient with diabetes)
amongst male patients. This tendency was even stronger in group 5 (patients treated with statins and glucose-lowering drugs) in both sexes (see Fig. 2, bottom line). To investigate the effect of insulin-sparing versus insulin-providing drugs in combination with statins, two additional groups of patients were analysed. We computed the composite cancer risk in a group of patients treated with insulin-sparing drugs and statins but not insulin-providing drugs, and in a second group of patients with insulin-providing drugs and statins but not insulin-sparing drugs. Amongst patients aged 50–60 years, there was a substantially stronger protective effect associated with statins in combination with insulin-sparing glucose-lowering drugs (men: OR 0.54, 95% CI: 0.47–0.61; women: OR 0.60, 95% CI: 0.51–0.71) compared to statins with insulin-providing glucose-lowering drugs (men: OR 0.70, 95% CI: 0.62–0.8; women: OR 0.77, 95% CI: 0.64–0.94).

Detailed results for female patients

For female patients treated with any glucose-lowering drugs (group 1) and insulin-sparing medications (group 2), there were no ORs for cancer risks that were significantly different from 1. For women treated with insulin-providing medications (group 3), there were significantly increased risks at 50–60 years of age for cancers of the pancreas (OR 5.9, 95% CI: 4.0–8.7) or kidney (OR 2.7, 95% CI: 1.5–4.9), secondary neoplasms in respiratory and digestive organs (OR 2.0, 95% CI: 1.6–2.7), and for all-site cancer (OR 1.4, 95% CI: 1.3–1.7). For female patients treated with statins and no glucose-lowering drugs (group 4), we found the strongest effects at ages 60–70 years with decreased risks for all-site cancer (OR 0.63, 95% CI: 0.60–0.66), as well as for a wide variety of specific sites including stomach, colorectum, liver,
pancreas, lung, skin, breast, uterus, ovary, kidney, brain, lymphoma and leukaemia with OR values between 0.3 and 0.7. For women at 60–70 years of age treated with statins and glucose-lowering drugs (group 5), the overall cancer risks were decreased (OR 0.72, 95% CI: 0.67–0.78), with ORs between 0.4 and 0.6 at 50–60 years of age for colon, rectal, lung, skin, breast, and ovarian cancers and secondary neoplasms.

**Detailed results for male patients**

For male patients treated with any glucose-lowering drug (group 1), we found at 50–60 years of age a decreased composite cancer risk (OR 0.81, 95% CI: 0.77–0.85) and a decreased risk for prostate cancer (OR 0.55, 95% CI: 0.50–0.61), whereas the risk was increased for cancer of the pancreas (OR 2.1, 95% CI: 1.7–2.5). There were also no sites with OR that were significantly different from 1 (group 2). For men treated with insulin-providing drugs in group 3, we observed the strongest effects at the ages of 40–50 years where the risks were decreased for prostate cancer (OR 0.34, 95% CI: 0.13–0.68) and increased for cancers of the colon, liver, pancreas, lung, and brain and secondary neoplasms, with OR values up to 8.7, and for all-site cancer (OR 1.6, 95% CI: 1.4–1.9). There were decreased composite cancer risks (at 50–60 years: OR 0.64, 95% CI: 0.61–0.67) for men treated with statins and no blood glucose-lowering drugs at sites including the tongue, tonsil, pharynx, oesophagus, stomach, colorectum, liver, pancreas, larynx, lung, skin, prostate, and bladder and non-Hodgkin’s lymphoma, myeloma, and leukaemia with ORs between 0.2 and 0.8. There was a protective effect for the composite cancer risk in patients treated with statins and glucose-lowering drugs (OR 0.64, 95% CI: 0.60–0.69), at sites including the stomach, colon, rectum, and lung and secondary neoplasms with ORs between 0.3 and 0.6.

**Regression analysis**

Table 1 shows the ORs from a logistic regression of the presence of statins and glucose-lowering drugs on composite cancer risks in both sexes. Significant results (P < 0.05) are shown in Table 1 in bold. The models account for 75% (83%) of the variation of the risks in female (male) patients; nonsignificant results for the Hosmer–Lemeshow tests indicate that the models are well calibrated. We found significantly increased risks for sulfonylureas and decreased risks for oral glucose-lowering drugs (such as metformin and rosiglitazone) and various statins.

Significant results (P < 0.05) from the regression analysis for site-specific ORs in female and male patients are shown in Fig. 3. The ORs and their 95% CI are also shown in the online Tables S1 and S2. The site-specific models showed on average somewhat lower adjusted R² values than the composite model (0.58 and 0.57 in female and male patients, respectively) and again nonsignificant results for the two Hosmer–Lemeshow tests (all P-values >0.88 for both tests). In female patients, we found that risks for cancer of the stomach, pancreas, colon, rectum, and kidney and non-Hodgkin’s lymphoma were typically increased in relation to treatment with insulin and sulfonylureas (with ORs up to 4.2), but decreased in combination with metformin and statins (ORs down to 0.21). Decreased risks were observed for cancers of the breast, ovary, and skin, multiple myeloma, and secondary neoplasms at lymph nodes and respiratory and digestive organs. Alpha-glucosidase inhibitors were associated with increased risk for non-Hodgkin’s lymphoma (OR 2.7, 95% CI: 1.4–5.4).

Some results, however, defied these general tendencies. For bladder cancer, we observed increased risks with rosuvastatin and glitazones, but decreased risks with fluvastatin. There was a harmful effect of glitazones in the kidney and of metformin in the uterus. From these results, only the relationships between metformin and the uterus (OR 1.7, 95% CI: 1.4–2.0, P < 0.001) and between glitazones and the bladder (OR 2.2, 95% CI: 1.2–3.9, P < 0.01) showed higher levels of significance.

We observed similar tendencies for male and female patients, with increased risks for cancer of the larynx, rectum, liver, and pancreas and leukaemia for sulfonylureas (ORs up to 3.0). The risk of pancreatic cancer was increased with insulin use (fast-acting, intermediate-acting and combined therapies with ORs up to 4.5). Fast-acting insulins increased the risk for liver cancer; combined insulin therapies also increased the risks for liver cancer as well as lymphoid leukaemia and laryngeal cancer. Long-acting insulins increased the risks for bladder and prostate cancer. Alpha-glucosidase inhibitors were associated with increased risks for laryngeal, liver and stomach cancer. A protective effect of metformin...
and statins was observed at several sites, including the larynx, prostate and pancreas, and for lymphoid leukaemia (ORs down to 0.31). We found decreased risks amongst statin users for cancers of the colon, lung, skin, and kidney and non-Hodgkin’s lymphoma and secondary neoplasms (lymph nodes and respiratory and digestive organs).

**Discussion**

Two different statistical approaches were used in the present study to clarify the relationship between prevalence of specific cancers and T2DM as well as anthyglycaemic and antihyperlipidemic treatment. The results of these two approaches are consistent with each other. We found higher cancer risks in patients treated with insulin-providing drugs for liver, lung, and secondary neoplasms in male patients and for pancreas in both sexes, but a lower risk for prostate cancer in men. The latter finding is in line with previous studies [2] and could be caused by lower testosterone levels in diabetic men [23, 24]. There is evidence to support diabetes as a genuine risk factor in the pathogenesis of liver and pancreatic cancers beyond the complex interplay of different risk factors, detection bias, cancer treatment and the effects of reverse causality as these cancers can also impair glucose metabolism [25–30]. In a meta-analysis, a twofold higher risk of hepatocellular carcinoma was seen in diabetic compared to non-diabetic subjects, with potential mechanisms including inflammation, cellular proliferation stimulated by hyperinsulinemia, high IGF-1 levels, and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>ORs (95% CIs) obtained from the logistic regression model for cancer risks for female and male patients</th>
</tr>
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<tbody>
<tr>
<td>Variable</td>
<td>Description</td>
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<tr>
<td>(Intercept)</td>
<td>2.5 (3.3–1.7)</td>
</tr>
<tr>
<td>A10AB</td>
<td>Insulin (fast-acting)</td>
</tr>
<tr>
<td>A10AC</td>
<td>Insulin (intermediate-acting)</td>
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<tr>
<td>A10AD</td>
<td>Insulin (combined fast- and long-acting)</td>
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<tr>
<td>A10AE</td>
<td>Insulin (long-acting)</td>
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<tr>
<td>A10BA</td>
<td>Metformin</td>
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<tr>
<td>A10BB</td>
<td>Sulfonylureas</td>
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<tr>
<td>A10BD</td>
<td>Combinations of oral blood glucose-lowering drugs</td>
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<tr>
<td>A10BF</td>
<td>Alpha-glucosidase inhibitors</td>
</tr>
<tr>
<td>A10BG</td>
<td>Glitazone</td>
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<tr>
<td>A10BH</td>
<td>DPP4 inhibitors</td>
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<tr>
<td>C10AA01</td>
<td>Simvastatin</td>
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<tr>
<td>C10AA02</td>
<td>Lovastatin</td>
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<tr>
<td>C10AA03</td>
<td>Pravastatin</td>
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<tr>
<td>C10AA04</td>
<td>Fluvastatin</td>
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<tr>
<td>C10AA05</td>
<td>Atorvastatin</td>
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<tr>
<td>C10AA07</td>
<td>Rosuvastatin</td>
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<tr>
<td>Age</td>
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<td>Adj. $R^2$</td>
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<td>$P_{HL \text{ fit}}$</td>
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<td>$P_{HL \text{ age}}$</td>
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We found significantly increased cancer risks for sulfonylureas and decreased risks for oral glucose-lowering drugs, glitazones, simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin for female and male patients, as well as decreased risks for metformin in men. The models account for 75% and 83% of the variation of the cancer risks in female and male patients, respectively, with highly nonsignificant $P$-values of the Hosmer–Lemeshow tests indicating that the models are well calibrated. $P_{HL \text{ fit}}$, $P$-value from Hosmer–Lemeshow tests examining whether the quality of the fit of the model differed according to the deciles of the fitted cancer risks; $P_{HL \text{ age}}$, $P$-value from Hosmer–Lemeshow tests examining whether the quality of the fit of the model differed according to age. ORs that are significantly different from one ($P < 0.05$) are shown in bold.
hyperglycaemia favouring development of steatosis and cirrhosis [25, 26]. Pancreatic cancer was also reported to be more common in diabetic subjects in whom it was suspected that hyperglycaemia may be the major mechanistic driver for this interrelation [27, 28]. Indeed, a dose–response meta-analysis revealed that every 0.56 mmol L\(^{-1}\) increase in fasting glucose was associated with a 14% increase in the rate of pancreatic cancer [29].

Together with data from cohort studies, all these results support the hyperglycaemia hypothesis based on findings of hyperglycaemia-induced DNA damage and hyperglycaemia-related induction of oxidative stress.

Despite this strong body of evidence, it is puzzling that several studies have shown that improved glycaemic control does not lead to reduced cancer risks [4, 6]. These findings suggest that different antihyperglycaemic drugs modify the diabetes-related and site-specific cancer risks in different ways. To understand how T2DM is related to cancer, it is necessary to understand not only the effects of a given antihyperglycaemic drug but also, more importantly, the effects of all possible combinations of such drugs on the observed cancer risks. This was the main purpose of the present study.

Recent studies provided evidence that metformin treatment, which is the first-line therapy in most patients with diabetes, was associated with a reduced incidence of various cancers. Metformin use reduced the risks of breast, colorectal and ovarian cancers in women, but decreased the risk of hepatocellular cancer in men [31–33]. However, the data are controversial. The few available randomized controlled trials on metformin could not confirm a reduced cancer risk in metformin users. A retrospective database analysis from Germany was also not able to confirm a reduced cancer risk in patients treated with metformin compared to sulfonylurea or insulin users [34]. In a retrospective cohort study from the UK [35], it was shown that metformin monotherapy carried the lowest risk of cancer, whereas the risk was increased in patients treated with a combination of metformin and sulfonylureas and even more so in those receiving sulfonylurea monotherapy or insulin. Our analysis confirms that metformin has an overall protective effect in male and female patients on the composite cancer risk, whereas the risk was increased in patients treated with a combination of metformin and sulfonylureas and even more so in those receiving sulfonylurea monotherapy or insulin. Our analysis confirms that metformin has an overall protective effect in male and female patients on the composite cancer risk, whereas sulfonylureas were associated with increased cancer risks. It is noteworthy that the mechanisms of potential anticancer effects of metformin are still unclear. Several molecular mechanisms may interact with signalling pathways.

Fig. 3 Relationships between medications (green circles) and the risks for cancer at specific sites (grey circles) for female (left) and male (right) patients. Results for the composite cancer risk are shown by the magenta node ('All'). Medications and cancers with a significant relation are linked by a line. The colours of the lines correspond to the values of the ORs obtained from the coefficients in the regression analyses. Blue lines indicate that patients with the given medication are at decreased risk for the given cancers, whereas red lines indicate increased cancer risks.
involved in cell growth and apoptosis such as activation of 5′adenosine monophosphate-activated protein kinase (AMPK) through the tumour suppressor protein kinase, liver kinase B1 [36]. Anti-neoplastic activities of metformin could be due to improvement of insulin sensitivity, inhibition of Akt/mTOR/p7OS6 signalling or an improved balance of adipokines (i.e., an increase in adiponectin and a decrease in leptin levels) [37].

Glitazones were related to lower malignancy risk in women with T2DM in a retrospective analysis of the Cleveland Clinic Diabetes Registry [38]. In another study of cancer incidence and glitazone therapy, sex differences were described with reductions only in women receiving rosiglitazone [39]. In the present analysis, we observed a modest but significantly protective effect of glitazones in both sexes, as recently reported [12]. In a population-based cohort study, decreased cancer risk was seen for many sites including the colorectum, breast, brain, uterus, stomach, prostate, kidney and lung, as well as lymphatic malignancies [40]. There are, however, sex- and site-specific differences. Whereas for men, there was only an overall protective effect, for women, we found increased risks for bladder and kidney cancer with glitazone use, but decreased risks for colon and skin cancer. Pioglitazone was indeed linked to an increased risk of bladder cancer in a meta-analysis of controlled studies [41].

We saw consistently increased cancer risks for both male and female patients receiving insulin-providing therapy. This is in line with the results of various epidemiological studies pointing towards higher cancer risk with sulfonylurea therapy [10, 34, 42]. However, studies comparing sulfonylurea with metformin therapy were not able to distinguish between potential protective effects of metformin and mitogenic effects of sulfonylurea therapy. In addition, it is unclear whether direct effects promoting cancer cell growth or indirect effects through induction of endogenous hyperinsulinemia may be involved. Furthermore, randomized control trials did not show a higher cancer risk in patients receiving sulfonylurea therapy [11]. In our analysis, sulfonylurea therapy was associated with increased cancer risks in both sexes with the highest effects for pancreatic cancer in women.

The use of insulin therapy has divergent effects depending on the agent and mode of action. We found that insulin therapy was typically linked to increased cancer risks, with the exceptions being a protective effect of combined insulin therapy on breast cancer in women and of fast-acting insulin on prostate cancer in men. Controversial results have been reported with regard to the risk of malignancies with insulin therapy and particularly with the long-acting insulin analog glargine which could have higher mitogenic potency than other insulins [2]. In our data set of T2DM patients, there was an insufficient number treated with glargine to be able to distinguish its effects from those of other long-acting insulins.

Statin therapy was found to be associated with lower prevalence rates of specific cancers and lower cancer mortality rates of low-grade resectable pancreatic adenocarcinoma or curatively resected colorectal cancers [17, 43, 44]. Anticancer effects were seen independently of the presence of diabetes [44, 45]. Several preventive effects on regulation of cancer cell proliferation and metastasis have been described in cell culture, animal models and humans: potential statin-induced mechanisms comprise changes in global tumour gene expression profiles, suggesting Mitogen-activated protein kinase (MAPK) pathway inhibition and pro-apoptotic effects as seen in breast cancer patients receiving atorvastatin therapy [46]. In the Women’s Health Initiative, use of lipophilic statins was associated with a 20% reduction in diagnosis of late-stage breast cancers and a marginally lower breast cancer mortality rate in postmenopausal women on statins [47]. Statin or antidiabetic drug therapy was not found to be related to a lower risk of any grade of prostate cancer [48]. Moreover, statin use was even associated with an elevated risk of a diagnosis of high-grade cancer. A meta-analysis of observational studies showed that statin use was associated with an approximately 15% lower risk of haematological malignancies [49]. A dose-response relationship was observed between statin use and reduced risk of cholangiocarcinoma in a population-based case-control study [50]. With regard to the risk of liver cancer, a nested case-control study found that statin use was associated with a 45% lower risk [45].

In the present study, we observed a lower risk of various cancers in patients receiving statins. Significant effects were found for all agents except lovastatin in both sexes. All agents had somewhat greater beneficial effects in men than in women with the largest effect observed in men treated with simvastatin, fluvastatin and rosuvastatin. In women, only rosvuastatin was associated with a
higher bladder cancer risk but further prospective studies are needed to investigate this association in more detail. Remarkably, we were able to show that the protective effect of statins more than offsets the increased cancer risks due to insulin-providing therapies. In fact, patients with diabetes treated with statins showed an overall decreased cancer risk when compared to patients not receiving antihyperglycaemic or antihyperlipidemic drugs.

Our data originate from the years 2006 and 2007 when evidence-based guidelines were not so strict as at present regarding target LDL cholesterol in patients with diabetes. At that time, statins were not yet a standard therapy for patients with diabetes. This allows us to isolate the influence of statin use on cancer risks with unprecedented precision. Our results show that besides the protective influence of certain insulin-sparing medications, a failure to control for statin use in patients with diabetes might lead to erroneous associations between antihyperglycaemic treatments and cancer. Consequently, in this regard, the results of all studies that do not explicitly control for statin use must be interpreted with caution. Of note, based on current recommendations, the majority of patients will need statin therapy. Therefore, current practical recommendations could contribute to reduce cancer risk in patients with diabetes although this hypothesis remains to be proven in large prospective studies.

A limitation of our analysis is the retrospective design and the lack of information on diabetes duration, duration of specific therapies, metabolic parameters (HbA1c and BMI) and lifestyle factors. To estimate the potential impact of several lifestyle factors, we repeated the regression analysis for the composite cancer risks by excluding all patients with a diagnosis of (i) obesity (ICD10 code E66), (ii) chronic obstructive pulmonary disease (COPD) as a proxy for smoking (ICD10 code J44) and (iii) alcohol-related disorders (ICD10 code F10). In each of these three cases, for both sexes, we obtained exactly the same significant associations as shown in Table 1, with similar or lower adjusted R² values (0.80–0.84 and 0.71–0.75 for male and female patients, respectively). We also found that our results were qualitatively independent of the choice of various thresholds used in the analysis, such as the choice of age groups or the number of patients required with a given combination of medications. Another limitation is the possibility of erroneously coded or missing diagnoses in the claims data, for example due to migration from or to Austria during 2006 and 2007. Although it might be possible that for instance patients in the control group are more likely to emigrate, this will mostly affect younger age groups with a low T2DM prevalence. That is, of the 155 432 and 205 005 persons who emigrated from or immigrated to Austria in 2006–2007, only 16.2% and 10.6% were more than 50 years old, respectively [51]. Therefore, effects due to migration are more likely to be observed at younger ages than those at which our main results were found.

The strength of our study lies in the large cohort size that is equivalent to all patients who have been hospitalized over 2 years in an entire country. This enables us to explicitly control for polypharmacy in patients by considering the combined use of many different diabetes drugs and statins. Therefore, to the best of our knowledge, this study is the first systematic investigation of the relation between diabetes and cancer that controlled for the influence of all possible antihyperglycaemic drugs and statins (according to ATC codes) and their combinations within the same patient sample. Our approach can be easily extended to unravel hitherto unknown associations between other types of diseases and drugs.

In conclusion, we found in a large data set of the Austrian population higher risks in diabetic versus nondiabetic subjects for liver, lung, and secondary cancers in men and for pancreatic cancer in both sexes, but a lower risk for prostate cancer in men. We obtained these results consistently in two independent statistical analyses. Statin therapy exerted a protective effect independently of sex, age and comorbid diabetes. Moreover, we observed age- and sex-dependent differences in site-specific cancers and in relation to antihyperglycaemic therapy. Insulin-sparing therapies (metformin and glitazones) were related to lower cancer risks, whereas insulin-providing therapies (sulfonylureas and glinides) were associated with higher risks in both sexes. Regarding insulin therapy, findings have been controversial, depending on sex, age, and the action and profile of the agent. Because of the overall higher cancer risk in patients with diabetes, the safety of all antihyperglycaemic drugs, including the risk of malignancies, should be carefully monitored.

Overall, by studying possible cancer–drug relations in patients with diabetes, we found that patients treated with insulin-sparing therapies are less likely to require cancer-related inpatient care. In
addition – though solely based on association studies – statins decreased the cancer risks in all patients with somewhat attenuated, but still beneficial, effects in patients with diabetes of both sexes and all ages. Further longitudinal studies, including of the impact of duration and dosage of specific therapies, are needed to clarify this important relationship.

Conflict of interest statement

No conflicts of interest to declare.

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Authors’ contributions

A.K.-W. wrote the manuscript and is the guarantor of the work. S.T. contributed to discussion, and reviewed and edited the manuscript. P.K. researched the data, contributed to discussion, and reviewed and edited the manuscript.

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Insulin-related cancer risk


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Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Results for the ORs and their 95% CI from the site-specific regression analysis for female patients.

**Table S2.** Results for the ORs and their 95% CI from the site-specific regression analysis for male patients.

**Figure S1.** ORs for female patients for the relations between site-specific cancer risks and different groups of medications compared to the control group. Sites with at least one significant result in any of the groups are shown. Each line corresponds to one site with the ORs for three different age intervals; significant results are shown in red.

**Figure S2.** ORs for male patients for the relations between site-specific cancer risks and different groups of medications compared to the control group. Sites with at least one significant result in any of the groups are shown. Each line corresponds to one site with the ORs for three different age intervals; significant results are shown in red.