Are Sulfonylurea and Insulin Therapies Associated With a Larger Risk of Cancer Than Metformin Therapy? A Retrospective Database Analysis

OBJECTIVE
Several meta-analyses of observational studies suggested that metformin use reduces cancer risk in type 2 diabetes. However, this result was not confirmed by the few available randomized controlled trials (RCTs), and many observational studies on metformin and cancer were potentially afflicted with time-related bias. We aimed to avoid this bias when comparing cancer incidence in users of sulfonylurea, insulin, and other diabetes medications, respectively, with cancer incidence in metformin users.

RESEARCH DESIGN AND METHODS
In a retrospective observational study, we used the German Disease Analyzer database with patient data from general practices throughout Germany. The study sample included 22,556 patients diagnosed with type 2 diabetes. During the median follow-up time of 4.8 years, 1,446 (6.4%) patients developed any cancer. In Cox regression analyses with either monotherapies or first diabetes medications as drug exposure, users of sulfonylurea (or insulin or other antidiabetes medications) were compared with metformin users.

RESULTS
In multivariable adjusted models, hazard ratios were 1.09 (95% CI 0.87–1.36) for sulfonylurea monotherapy, 1.14 (95% CI 0.85–1.55) for insulin monotherapy, and 0.94 (95% CI 0.67–1.33) for other diabetes medications compared with metformin monotherapy. Results were similar for comparison of first diabetes medications.

CONCLUSIONS
In a retrospective database analysis, taking into account potential time-related biases, no reduced cancer risk was found in metformin users. To clarify the association between diabetes medication and cancer risk, further well-designed observational studies and RCTs are needed.

From meta-analyses, there is evidence that type 2 diabetes is associated with an increased risk of cancer (1–4). Antidiabetes medication may modify cancer risk in patients with type 2 diabetes. Several meta-analyses suggested that metformin reduces the risk of cancer by approximately one-third (5–9). In one recent meta-analysis, for example, a 34% reduction in the incidence of any cancer and a 33%
reduction in cancer mortality were reported (7). However, studies of the effects of drugs are prone to bias, and recently, Suissa and Azoulay (10) claimed that 23 observational studies on the effects of metformin on cancer incidence were potentially afflicted with time-related bias. The finding of a reduced cancer risk in persons taking metformin might be also put into question because the few randomized controlled trials (RCTs) published so far have failed to confirm the results of the observational studies (11,12).

In observational studies on the association of diabetes medication and cancer risk, several kinds of time-related bias may occur: immortal time bias, time-window bias, and time-lag bias (10,13,14). According to Suissa and Azoulay (10,13,14), a large number of studies are afflicted with the immortal time bias. In cohort studies, for instance, immortal time bias occurs if the time between entry into the cohort and first use of the drug of interest is misclassified as exposed, although this part of the follow-up time is by design free of incident cancer. Subjects with cancer prior to first drug use would be excluded from analyses, so there is a guarantee of survival for the time between cohort entry and first drug use. Therefore, if metformin users are compared with nonusers, immortal time bias results in an underestimate of the true cancer risk in metformin use.

For the current study, we use longitudinal data from general practices throughout Germany. The aim is to compare the risk of cancer in patients taking sulfonylurea, insulin, or other diabetes medication other than metformin, respectively, with the risk of cancer in patients taking metformin and to avoid the kinds of bias mentioned above.

RESEARCH DESIGN AND METHODS

Study Population, Assessment of Variables

We used the German Disease Analyzer database (IMS Health), which includes patient data entered by general practices throughout Germany (15–17). Practices are anonymously reporting all diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical [ATC] Classification System), hospital admissions, and laboratory test results on an ongoing basis. The current study sample included 22,556 patients from 1,143 practices who received a diagnosis of type 2 diabetes during the index period used for this study (January 2000 to December 2012) and who used any diabetes drug after diagnosis of diabetes. Follow-up was until August 2013. Persons were censored when they died, changed their general practitioner (GP), moved, or disappeared or when the end of follow-up was reached. The main outcome measure was cancer incidence (ICD-10 C00–C97) recorded in the database between the index date and end of follow-up. Patients for whom the first diabetes medication was prior to the first diagnosis of diabetes were excluded from analyses because this is implausible and probably due to a false documentation by GPs. Furthermore, patients were excluded from analyses when a first diagnosis of cancer was prior to the first diagnosis of diabetes. The validity and representativeness of the Disease Analyzer database have been assessed previously (18).

Demographic data included age, sex, health insurance (private/statutory health insurance), and practice region (East/West Germany). Obesity diagnosis, lipids disorders, hypertension, use of anti-hypertensives, use of lipid-lowering agents, use of antithrombotic agents, vaccination (ATC J07), and prevalence of microvascular complications (retinopathy, neuropathy, or nephropathy) were assessed as potential confounders. Obesity diagnosis most likely reflects severe or morbid obesity as assessed by GPs. Baseline data on BMI were only available for a small subgroup (<30%) and were not considered. Lipid disorders were defined by ICD 10 code E78. Hypertension was defined by ICD 10 code I10. Furthermore, a revised version of the Charlson comorbidity index was used as generic marker of comorbidity (19). Covariates were measured at maximum 2 or 3 years before diagnosis of diabetes.

Statistical Methods

Characteristics of the study group were shown for the whole sample and according to first diabetes medication. Characteristics of the study participants were compared between users of different first diabetes medication using χ² tests in case of binomial proportions and the F-test for age.

Two kinds of comparisons were made. In a first group of comparisons (intention-to-treat), patients with sulfonylurea (or insulin or other medications except metformin, respectively) as their first diabetes medication were compared with patients with metformin as their first diabetes medication. Persons with more than one first diabetes medication were excluded from these analyses. In intention-to-treat analyses, we only looked at the first diabetes medication irrespective of changes later in therapy. For all four groups, time 0 was the time 1 year after the first prescription of the respective medication.

In a second group of comparisons (monotherapies), patients with a monotherapy of sulfonylurea, insulin, or other medications except metformin, respectively, were compared with patients with a metformin monotherapy. Monotherapy means in our study that patients only used one diabetes medication throughout their whole therapy without switching to another drug or using several drugs at a time. For all four groups, time 0 was the time 1 year after the first prescription of the respective medication.

For intention-to-treat and for monotherapies, crude cancer rates, i.e., number of incident cancer cases per person-year, were calculated for all four groups of diabetes medication. From the crude rates, crude rate ratios were calculated to compare users of sulfonylurea, insulin, and other medications with users of metformin.

Furthermore, Cox regression analyses were carried out as intention-to-treat and monotherapies, and hazard ratio (HR) and 95% CI were calculated to compare users of sulfonylurea, insulin, and other medications with users of metformin. For each comparison of diabetes medications, five different models were fitted: 1) an unadjusted model (crude model); 2) a model adjusted for age, sex, health insurance (private or statutory), and practice region (i.e., Western or Eastern Germany); 3) model 2 + time from first diagnosis of diabetes until prescription of first diabetes medication; 4) model 3 + obesity, hypertension, hyperlipidemia, and Charlson index; and 5) model 4 + use of antihypertensives, use of lipid-lowering agents, use of antithrombotic agents, vaccination (ATC J07), and prevalence of
users and users of the comparison group. The variance inflation factor was calculated as $1 / (1 - R^2) = 1 / 0.94$ where $R^2$ refers to the regression of all covariates on metformin. To assess $\psi$, the probability of no censoring, we used data of the German Center for Cancer Registry Data, at the Robert Koch Institute, Berlin, Germany (21), and we assumed an increased cancer incidence in subjects with diabetes ($HR = 1.25$).

The power calculations led to the following results. For comparison of first therapies (Table 2), the following risk reductions in metformin users could be detected: 21% (sulfonylurea vs. metformin), 32% (insulin vs. metformin), and 26% (other diabetes drugs vs. metformin). For comparison of monotherapies (Table 3), detectable risk reductions were as follows: 33% (sulfonylurea vs. metformin), 41% (insulin vs. metformin), and 38% (other diabetes drugs vs. metformin).

As a sensitivity analysis, Cox regression analyses for cancer of all sites were repeated with a redefinition of time 0, which was now set at 3 years after first prescription of diabetes medication.

The level of statistical significance was 5%. The analyses were carried out using SAS version 9.3.

RESULTS

The mean follow-up after first diagnosis of diabetes until incidence of cancer or end of observation was 4.8 years. Among 22,556 patients included in the analyses, 1,446 (6.4%) developed cancer after diagnosis of diabetes (Table 1). Metformin was the most frequently used diabetes medication; 82% of all patients ever had a prescription of metformin. As expected, metformin was mostly used as a first-line diabetes medication. Among 18,851 patients who ever used metformin, 15,786 (83.7%) used it as their only first diabetes medication. In

<table>
<thead>
<tr>
<th>Table 1—Sample characteristics of participants</th>
<th>First diabetes medication$^{a,b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Metformin$^b$</td>
</tr>
<tr>
<td>$n = 22,556$</td>
<td>$(n = 15,786)$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.0 ± 9.6</td>
</tr>
<tr>
<td>Male sex ($n, %$)</td>
<td>11,339 (50.3)</td>
</tr>
<tr>
<td>Practice region</td>
<td>16,908 (75.0)</td>
</tr>
<tr>
<td>Western Germany ($n, %$)</td>
<td>16,908 (75.0)</td>
</tr>
<tr>
<td>Eastern Germany ($n, %$)</td>
<td>5,648 (25.0)</td>
</tr>
<tr>
<td>Insurance</td>
<td>1,480 (6.6)</td>
</tr>
<tr>
<td>Private health insurance ($n, %$)</td>
<td>21,076 (93.4)</td>
</tr>
<tr>
<td>Statutory health insurance ($n, %$)</td>
<td>77 (0.3)</td>
</tr>
<tr>
<td>Charlson index</td>
<td>10,152 (45.0)</td>
</tr>
<tr>
<td>Microvascular complications ($n, %$)</td>
<td>1,098 (4.9)</td>
</tr>
<tr>
<td>Hypertension ($n, %$)</td>
<td>16,824 (74.6)</td>
</tr>
<tr>
<td>Use of antihypertensives ($n, %$)</td>
<td>16,126 (71.5)</td>
</tr>
<tr>
<td>Dyslipidemia ($n, %$)</td>
<td>10,152 (45.0)</td>
</tr>
<tr>
<td>Use of lipid-lowering agent ($n, %$)</td>
<td>5,861 (26.0)</td>
</tr>
<tr>
<td>Use of antithrombotic agents ($n, %$)</td>
<td>5,539 (24.6)</td>
</tr>
<tr>
<td>Obesity diagnosis ($n, %$)</td>
<td>4,354 (19.3)</td>
</tr>
<tr>
<td>Vaccination ($n, %$)</td>
<td>346 (1.5)</td>
</tr>
<tr>
<td>Ever use of diabetes medication$^a$</td>
<td>Metforminb</td>
</tr>
<tr>
<td>$n = 22,556$</td>
<td>15,786 (83.7)</td>
</tr>
<tr>
<td>Insulinb</td>
<td>5,970 (26.5)</td>
</tr>
<tr>
<td>Other</td>
<td>6,135 (27.2)</td>
</tr>
<tr>
<td>Incidence of cancer ($n, %$)</td>
<td>1,446 (6.4)</td>
</tr>
</tbody>
</table>

$^a$Use of diabetes medication after diagnosis of cancer was not taken into account. $^b$Patients who used more than one drug as first diabetes medication were not included. $^c$P values refer to global comparisons of first diabetes medications.
contrast, sulfonylurea and insulin were often used as second- or third-line medications, and only 2,879 (48.2%) among 5,970 ever users of sulfonylurea had it as their only first diabetes therapy. Persons with metformin as first diabetes drug were younger, had fewer microvascular complications of diabetes, and had more frequent diagnoses of hypertension, dyslipidemia, and obesity than users of other drugs as first diabetes medication.

Compared with patients with metformin as first diabetes medication, no increased risks of cancer of all sites were found in patients with other first diabetes medications, i.e., either sulfonylurea, insulin, or other medication but metformin (Table 2). In fully adjusted models, the corresponding HRs were 1.01 (95% CI 0.88–1.13) to 0.88 (95% CI 0.69–1.12]) for the comparison of sulfonylurea as first therapy with metformin as first therapy. For the comparison of sulfonylurea monotherapy with metformin monotherapy, HR was 1.13 (95% CI 0.79–1.60) for the full model without HbA1c, and it was 1.11 (95% CI 0.78–1.59) after addition of HbA1c to the model.

When the starting point of exposure was set at 3 years after first prescription of diabetes medications, HRs for the comparison of first diabetes medications were as follows: 0.99 (95% CI 0.82–1.20) for sulfonylurea, 0.89 (95% CI 0.62–1.28) for insulin, and 0.80 (95% CI 0.59–0.90) for other medication but metformin (reference: metformin as first diabetes medication).

**CONCLUSIONS**

None of our analyses showed that the risk of cancer of all sites was lower in users of metformin than in users of other diabetes medications. In intention-to-treat type analyses, we compared first diabetes medications—irrespective of later changes in medication—and we compared persons with different diabetes monotherapies, and in both types of analyses, the null results were virtually the same.

This contrasts with the bulk of other studies. Several meta-analyses suggested that use of metformin is associated with a lower risk of cancer. However, following Suissa and Azoulay (10,14), these meta-analyses were largely based on studies that might be afflicted with time-related bias. Suissa and Azoulay (10) assessed 26 observational studies on metformin and cancer and found indication of biases in 23 of these studies. Only in the most recent meta-analysis on metformin and overall cancer, the authors admit that some of the observational studies included in their meta-analysis may be biased (9). However, they state that an assessment of time-related bias was not in the scope of their work.

In the following, we first discuss how we coped with problems from time-related bias and then compare our results with those of some other observational studies and RCTs.

**Avoiding the Immortal Time Bias**

In most published studies on metformin and cancer risk, metformin users are...
compared with nonusers. Misclassification of the time before the first prescription of metformin, which is by design free of cancer, may lead to an immortal time bias and an underestimate of cancer risk in metformin users. In half of the 26 observational studies included in their study, Suissa and Azoulay (10) found immortal time bias. They suggested two approaches to avoid this bias.

One is to do time-dependent Cox regression analyses. This means that time before first description of diabetes medication is considered as unexposed. Thus two statuses are compared: the exposure status refers to the follow-up time after first medication, whereas the status of nonexposure includes the time of observation for those who did not use the considered medication and, in addition, the time before first medication for those who used the medication. The other approach is of the intention-to-treat type, i.e., patients are considered exposed after the first prescription of diabetes medication, regardless of whether they switch to other medications or not. In our view, the first approach has two drawbacks. If the time before first prescription of diabetes medication that is immortal is considered as nonexposed this might as well lead to an underestimate of risk for those who do not use the considered medication. Besides, a comparison of users of metformin with nonusers is difficult to interpret because nonusers of metformin might be a quite heterogeneous group covering various alternative ways of therapy. Therefore, we carried out intention-to-treat type analyses. As this kind of analysis also has some drawbacks because it is unclear how patients are treated after first diabetes medication, we also compared monotherapies. In both types of analysis, we only considered time periods after first medication as exposed. So we did not include times before medication and thus made sure that the immortal time bias could not occur in our analyses.

**Avoiding Bias From Time Lag**

Another potential bias observed in studies on associations between diabetes medication and cancer refers to confounding by disease duration. Metformin is often used as a first-line medication, whereas sulfonylurea and insulin are often used as second- or third-line therapies. Thus patients who receive sulfonylurea or insulin often have longer durations of diabetes and thus an increased risk of cancer irrespective of their age. A bias from comparing second- or third-line therapies with first-line therapies could not occur in our analyses, because we considered only the first medication of each patient. However, disease duration could still differ even between patients with different monotherapies or different first diabetes medications. Therefore, we adjusted for diabetes duration in the Cox regression models.

**Other Observational Studies**

Our results contrast strongly with those of most other studies, and one important reason may be that we made efforts
to avoid time-related bias. In particular, immortal time bias was not possible in our analyses, because only times after drug prescription were included. There are few published studies on use of diabetes drugs and cancer incidence that were explicitly designed to avoid time-related bias. In a study on metformin drug use and colorectal cancer incidence, only times after first prescription of diabetes drugs were included, and latency times were accounted for (23). In another study on pioglitazone use and cancer incidence, time-dependent Cox regression analyses were done (24). Interestingly, in both studies, no associations between drug use and cancer risk were observed, which is in line with our null results. In a further study linking dispensing records from pharmacies to hospital discharge records, cancer risk in metformin users was compared with cancer risk in sulfonylurea users, and a risk reduction of 10% was reported for metformin use (HR = 0.90 [95% CI 0.88–0.91]) (25). A sensitivity analysis only with monotherapies led to virtually the same results. In that study, time-related bias was avoided, but there might be a selection bias because patients with diabetes who are not treated in hospital are not included in the database. In a recently published observational study, new users of metformin and new users of sulfonylureas were compared with regard to the incidence of bladder cancer (26). The authors attached much importance to avoid different types of time-related bias. In particular, immortal time bias was avoided by using the date of the second prescription as the index date. Metformin use was not associated with a decreased risk of bladder cancer in a fully adjusted model (HR = 0.81 [95% CI 0.60–1.09]), which is in line with the results of the current study.

Randomized Controlled Studies
Compared with observational studies, the potential of bias is reduced in RCTs. Using data of the ADOPT (A Diabetes Outcome Progression Trial) and the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials, a metformin group was compared with a rosiglitazone and a glibenclamide group, respectively, and moreover, a sulfonylurea group was compared with a metformin group (11). Statistically significant associations between drug use and cancer incidence were found in none of these comparisons. In a meta-analysis of RCTs, metformin was compared with any comparator (pioglitazone, rosiglitazone, glibenclamide, sitagliptin, usual care, placebo), and the overall HR was 1.02 (95% CI 0.82–1.26) (12). The authors admit that the follow-up times of the included studies were quite short and that the comparators were heterogeneous, but nevertheless, this meta-analysis contrasts strongly with most observational studies.

Limitations and Strengths
Some limitations of our study have to be mentioned. First, our measures of drug exposure were quite simple. First description of diabetes medication in an intention-to-treat-type analysis neglects later changes in diabetes medication. The problem of changes in diabetes medication does not come up in our second type of analysis, which was confined to monotherapies. However, if patients stick to their first diabetes medication, this might indicate that their therapy is successful and that their control of glycaemia works well. Thus patients with monotherapies might differ from patients with changes in medication and might not be representative for the whole group of patients with diabetes. Even so, the main result—no association between type of diabetes medication and incidence of cancer—was the same for both types of analysis. Second, the mean time of observation after first diagnosis of diabetes was only ~5 years, and this means that we mainly assessed associations of diabetes medication with promotion of cancer rather than associations with induction of cancer. Third, residual confounding, confounding by indication, and differences in adherence to regimen cannot be fully ruled out in our study. Fourth, the maximum of diabetes duration in our study was 13.6 years, and people with very long diabetes duration are not included in the database. Fifth, retrospective primary care database analyses are, in general, limited by the validity and completeness of data. As an example, all patients included in the study population were diagnosed with type 2 diabetes by GPs, but we cannot exclude that some patients with type 1 diabetes had been misclassified as having type 2 diabetes by GPs. However, in view of the low prevalence of type 1 diabetes (~5% of all diabetes cases), this might affect only a very small proportion of patients, which is unlikely to bias our results. This applies even stronger for maturity-onset diabetes of the young, which is still much less prevalent than type 1 diabetes. Also, assessment of comorbidity relied on ICD-10 codes by primary care physicians only. Data on socioeconomic status (e.g., education, income) and lifestyle-related risk factors (e.g., smoking, alcohol, physical activity) were also lacking. Data on BMI were only available for a subgroup at baseline, but we believe that diagnosis of obesity given for all patients captures a lot of the information of the BMI with regard to an increased risk of diabetes. HbA1c was available for only half of the patients, but for this subgroup, additional adjustment for HbA1c had a negligible effect on the association between diabetes medication and cancer risk.

An important strength of our study is that we avoided some kinds of bias that appear in various other studies on the association between diabetes medication and incidence of cancer. As described above, immortal time bias was excluded in our types of analyses, we took different time-lag periods into account, and we adjusted for duration of diabetes. Another strength is the use of real-world data on prescriptions and diagnoses in primary care practices where the majority of type 2 diabetes patients are treated. All prescriptions are continuously documented, allowing unbiased exposure assessment (no recall bias).

Conclusion
In our study, we made efforts to avoid immortal time bias and bias from time lag and latency. The null results from our analyses are in line with the results from three other studies that also avoided these kinds of bias and with results from the few RCTs carried out so far. There is a strong need for further studies on the association between diabetes medication and incidence of cancer that take into account the many methodological problems occurring in pharmacological epidemiology. Moreover, we suggest well-powered analyses avoiding time-related biases to assess associations...
between diabetes medication and site-specific cancer, in particular, colorectal, breast, pancreatic, liver, and hepatocellular cancer.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** B.K. researched data and wrote the manuscript. W.R. planned the study, contributed to the discussion, and reviewed the manuscript. K.K. contributed to the discussion and reviewed the manuscript. W.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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