Lower Risk of Cancer in Patients on Metformin in Comparison With Those on Sulfonylurea Derivatives

Results From a Large Population-based Follow-up Study

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OBJECTIVE—Numerous studies have suggested a decreased risk of cancer in patients with diabetes on metformin. Because different comparison groups were used, the effect magnitude is difficult to estimate. Therefore, the objective of this study was to further analyze whether, and to what extent, use of metformin is associated with a decreased risk of cancer in a cohort of incident users of metformin compared with users of sulfonylurea derivatives.

RESEARCH DESIGN AND METHODS—Data for this study were obtained from dispensing records from community pharmacies individually linked to hospital discharge records from 2.5 million individuals in the Netherlands. The association between the risk of cancer in those using metformin compared with those using sulfonylurea derivatives was analyzed using Cox proportional hazard models with cumulative duration of drug use as a time-varying determinant.

RESULTS—Use of metformin was associated with a lower risk of cancer in general (hazard ratio 0.90 [95% CI 0.88–0.91]) compared with use of sulfonylurea derivatives. When specific cancers were used as end points, similar estimates were found. Dosage-response relations were identified for users of metformin but not for users of sulfonylurea derivatives.

CONCLUSION—In our study, cumulative exposure to metformin was associated with a lower risk of specific cancers and cancer in general, compared with cumulative exposure to sulfonylurea derivatives. However, whether this should indeed be seen as a decreased risk of cancer for the use of metformin or as an increased risk of cancer for the use sulfonylurea derivatives remains to be elucidated.

As the drug of first choice in type 2 diabetes mellitus, metformin is the most widely prescribed oral glucose-lowering drug (OGLD) (1,2). However, the decision to prescribe metformin also depends on patient characteristics: metformin use is contraindicated in those with renal failure, cardiac, or hepatic failure (2).

A statistically nonsignificant relationship between use of metformin and the risk of colon cancer was described in 2004 (3). However, 1 year later, metformin was found to be associated with a decreased risk of cancer in general in a case-control study in a diabetic population (4). Numerous studies followed; among which studies confirming the association between use of metformin and a decreased risk of cancer in general (5–8) or in specific cancers (5,6,9–14). However, for breast cancer (5,6) and prostate cancer (5,14), the decreased risk was not consistently demonstrated; for other cancers, no association with use of metformin was found (6,12). Hence, there is heterogeneity among published studies on cancer in patients with diabetes on metformin (15), partly because different comparison groups were used, such as nonmetformin users, users of other OGLD, or users of insulin. Higher endogenous insulin levels have been linked to an increased risk of certain cancers (16). Moreover, specifically for insulin glargine, the debate whether this specific insulin increases the risk of cancer is ongoing (17–21).

Owing to factors such as different drugs used to attain metabolic control, the duration of diabetes, and the presence of other diseases, the assessment of cancer risk in diabetic patients remains difficult. Therefore, the objective of this study was to analyze whether, and to what extent, use of metformin is associated with a decreased risk of cancer in a cohort of incident users of metformin compared with use of sulfonylurea derivatives.

RESEARCH DESIGN AND METHODS

Setting

Data for this study were obtained from the PHARMO Record Linkage System (RLS), which includes drug-dispensing records from community pharmacies linked at a patient level to hospital discharge records from the Dutch National Medical Register for approximately 2.5 million individuals in the Netherlands since 1986. The drug-dispensing database contains detailed information for prescriptions as of 1998. The hospital record database

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contains information on discharge diagnoses and the dates of admission and discharge, coded according to the ICD-9.

Study population

All individuals with more than one prescription for any hypoglycemic drug between 1 January 1998 and 31 December 2008 were eligible. To ensure a study cohort of incident OGLD users, participants needed to have a 6-month period without a prescription for any hypoglycemic agent before inclusion. Patients using only insulin, those who started taking OGLDs other than biguanides or sulfonylurea derivatives, those aged younger than 18 years at the first prescription, and those with a primary cancer before the first prescription of an OGLD were excluded from the analysis as well.

Exposure

The OGLDs were classified into two mutually exclusive categories according to Anatomical Therapeutic Chemical classification code: biguanides (A10BA) and sulfonylurea derivatives (A10BB). In the Netherlands, metformin is the only biguanide available. To obtain a valid estimate, use of sulfonylurea derivatives was chosen as the comparator because, in our opinion, a comparison should be made with participants with diabetes to reduce the risk of confounding by indication. In addition, one drug category for the same indication, and of sufficient size, is the most straightforward comparator. Besides metformin, sulfonylurea derivatives are most frequently used.

The cumulative exposure to each OGLD category was calculated for each participant in days since the start of the respective OGLD type until death of the participant, diagnosis of cancer, removal from the PHARMO RLS catchment area, the last day of use of a dispensing agent in the same OGLD category, start of insulin or another OGLD than metformin or sulfonylurea derivatives, or end of the study period at 31 December 2008.

To visualize drug adherence, the percentage of participants adherent to therapy was calculated: for every month of follow-up, the number of users of each drug was divided by the total number of users of that drug at study start.

Outcome

The primary outcome was first hospital admission with a primary diagnosis of any type of cancer, ICD-9 codes 140–172, 174–209, and 235–239. Subanalyses were performed for the following specific cancers (ICD-9 code): esophagus (150), stomach (151), colorectal (153–154), primary liver (155), pancreatic (157), respiratory tract (160–165), breast (174–175), and prostate (185). These cancers were selected because they have been previously studied in association with the use of metformin.

Covariables

Age at first OGLD prescription, sex, number of unique other drugs used in the year before the start of OGLD, number of hospitalizations in the year before the start of OGLD, and calendar time were considered as potential confounders or effect modifiers. For each dispensing, the dosage was available. The average dosage was calculated for metformin and sulfonylurea derivatives as the average defined daily dosage (DDD) over the previously dispensed prescriptions.

Statistical analysis

The association between metformin and cancer was analyzed using Cox proportional hazards models, with duration of cumulative drug use as a time-varying determinant, as described earlier (22). In this model, cumulative exposure to metformin in participants with cancer at the date of diagnosis was compared with cumulative exposure to sulfonylurea derivatives in the remaining cohort members at the same date of follow-up (i.e., with the same duration of OGLD exposure in days). Time since the start of OGLD was used as the underlying timescale in the Cox proportional hazard model. Participants were censored at the time they started insulin or another OGLD than the drug of interest (metformin) or the reference drugs (sulfonylurea derivatives); in case of multiple cancer diagnoses, additional censoring occurred at the first cancer.

Subanalyses. Different subanalyses were performed to assess the robustness of the results. To address possible reverse causation, a latency period was taken into account (subanalysis A); we assumed that cancer was already present 1 year before it was actually diagnosed (i.e., end of cumulation of exposure on 21 June 2007 when the cancer was diagnosed at 21 June 2008). To assess the effects of long-term use, another subanalysis was performed in patients using metformin or sulfonylurea derivatives for at least 365 days (subanalysis B). Because metformin users are frequently additionally treated with sulfonylurea derivatives and vice versa, a subanalysis was performed in which additional censoring of the participants took place at the moment that participants taking metformin started on sulfonylurea derivatives and the moment participants on sulfonylurea derivatives started on metformin (subanalysis C). Furthermore, a subanalysis was performed in those who were solely treated with monotherapy with metformin or sulfonylurea derivatives (subanalysis D), and a subanalysis was performed in those who were treated with metformin as well as with sulfonylurea derivatives but not with any other hypoglycemic drug during the study period (subanalysis E).

Also, the effect of dosage was assessed in additional analyses in which the full model was adjusted for dosage in a time-dependent manner. However, because follow-up information was used to perform this analysis, a second analysis was performed in which the full model was stratified for the dosage of the first OGLD. In these analyses, those with a higher-than-the-mean first dosage of metformin were compared with those with a higher-than-the-mean first dosage of sulfonylurea derivatives. In addition, those with a lower-than-the-mean first dosage of metformin were compared with those with a lower-than-the-mean first dosage of sulfonylurea derivatives.

Third, a dosage analysis was performed within, respectively, users of metformin and sulfonylurea derivatives in which the average DDD during follow-up in those with cancer was compared with the average DDD in all individuals without cancer.

General statistics. Covariables that changed the hazard ratio (HR) of cancer risk by more than 10% or were considered clinically relevant were included in the model. To test for effect modification, interaction terms were introduced in the model, and stratified analyses were performed. Nonparametric tests (Kruskal-Wallis) and linear regression were applied to verify differences between the treatment groups for continuous variables. These were preferred over ANOVA because there was no equality of variance among the different treatment groups. Differences in categoric variables between the groups were tested with a χ^2 test. Analyses were performed using SAS 9.2 software (SAS Institute, Inc., Cary, NC). *P* values are two-sided and were considered statistically significant at $P < 0.05$.

RESULTS—Within the PHARMO RLS, 158,599 participants were prescribed an

OGLD or insulin between 1 January 1998 and 31 December 2008; of these, 3,184 (2.0%) were excluded due to inconsistencies in the database and 6,638 (4.2%) for having a cancer diagnosis before 1 January 1998 or before exposure. Another 14,016 (8.8%) were solely treated with insulin, and 47,997 (30.3%) did not have a prescription-free period of 6 months before starting on OGLD. Another 1,390 participants (0.9%) were exposed before the age 18 years, and 1,866 (2.1%) had their first prescription for an OGLD other than metformin or a sulfonylurea derivative. After applying exclusion criteria, 85,289 participants (53.8%) were included in the study cohort (participants could be excluded for several reasons).

Between participants starting metformin and those starting sulfonylurea derivatives, significant differences were present at baseline and during follow-up (Table 1). Although those prescribed metformin were significantly younger, the age distribution was comparable between users of metformin and sulfonylurea derivatives. Patient starting with metformin used fewer other drugs and had fewer hospitalizations in the year before starting OGLD than those starting sulfonylurea derivatives. The duration of follow-up since the first OGLD was significantly shorter for those who started with metformin than for those who started with sulfonylurea derivatives. An adherence curve is presented in Supplementary Figure 1; the difference in adherence to therapy between those on metformin and those on sulfonylurea derivatives was statistically significant (P value $<$ 0.001), with those on metformin being less adherent.

Of the 3,552 participants hospitalized for cancer, 1,590 started with metformin and 1,962 started with sulfonylurea derivatives. The incidence rates were, respectively, 10.69 and 12.96 cancers per 1,000 patient-years. Cumulative exposure to metformin was associated with a lower risk of cancer compared with cumulative exposure to sulfonylurea derivatives (HR 0.90 [95% CI 0.88–0.91]; Fig. 1). In the full model, adjustments were made for age at first OGLD prescription, sex, calendar time, number of unique drugs used, and number of hospitalizations in the year before the start of OGLD (0.90 [0.89–0.91]). Further adjustments by adding dosage as an additional time-varying covariable to the model yielded a similar HR of 0.90 (0.89 – 0.91). Because follow-up information is used when applying this method, stratified analyses for baseline dosage were also calculated (Fig. 1). In these analyses, those with a dosage higher than the median dosage had a lower hazard (0.87 [0.85–0.88]) than those starting on a dosage lower than the median dosage (0.91 [0.89–0.93]).

Different subanalyses were performed to test the robustness of the results (Fig. 1); the HR did not change more than 10% in any of these analyses. The full model was further analyzed stratified for those older than the median age and those younger. For those younger than the median age, a lower HR for the risk of cancer (HR 0.86 [95% CI 0.84–0.88]) was found than for those aged older (0.93 [0.91–0.95]). In addition, the full model was analyzed stratifying for those who had been hospitalized before the start of OGLD versus those who had not been hospitalized. Those hospitalized before the first dispensing of OGLD had a lower risk of cancer (0.84 [0.81–0.87]) than those not hospitalized (0.91 [0.89–0.92]).

The full model was applied in all subanalyses in which specific cancers were used as end points as well; these results are presented in Table 2. As with the analysis on cancer in general, additional adjustment by average DDD did not change the point estimate. Furthermore, for all specific cancers, a baseline dosage of more than the median also had a slightly higher protective effect than a baseline dosage of less than the median. Exposure of

Table 1—*Characteristics of participants using metformin or sulfonylurea derivatives*

Characteristic	Incident users of	
	Metformin	Sulfonylurea derivatives
Patients, *n* (%)	52,698 (61.8)	32,591 (38.2)
Age at first prescription of OGLD in years*	61.8 (13.4)	65.6 (13.8)
	62.1 (52.8–71.7)	66.7 (56.2–76.0)
Male sex, *n* (%)†	24,432 (46.4)	15,699 (48.2)
Unique other drugs (*n*) used in the year before first prescription of OGLD*	6.0 (4.8)	6.1 (5.3)
	5 (2–8)	5 (2–9)
Unique hospitalizations (*n*) in the year before first prescription of OGLD*	0.3 (0.8)	0.3 (0.9)
	0 (0–0)	1 (0–1)
Duration of follow-up since first OGLD prescription (days)*	1,031 (853)	1,697 (1,071)
	825 (348–1,526)	1,639 (791–2,534)
Average daily dosage		
Of the first OGLD prescription in DDD*	0.55 (2.17)	1.04 (0.91)
	0.45 (0.25–0.50)	0.67 (0.50–1.33)
Over all OGLD prescriptions since first prescription in DDD*	0.69 (1.73)	1.49 (1.13)
	0.50 (0.38–0.85)	1.14 (0.65–2.00)
Solely treated with metformin or sulfonylurea derivatives, *n* (%)	27,129 (51.5)	13,045 (40.0)
Additional treatment with metformin or sulfonylurea derivatives, *n* (%)	19,068 (36.2)	16,950 (52.0)
Hospitalized for cancer diagnosis, *n* (%)	1,590 (3.0)	1,962 (6.0)
Censored because of death, *n* (%)	6,501 (12.3)	3,459 (10.6)
Censored because of start of other OGLD or insulin, *n* (%)	11,909 (22.6)	8,781 (26.9)

Data are expressed as mean (SD) or median (interquartile range) unless otherwise indicated. * P value after linear regression <0.001. †P value after χ^2 test <0.001.

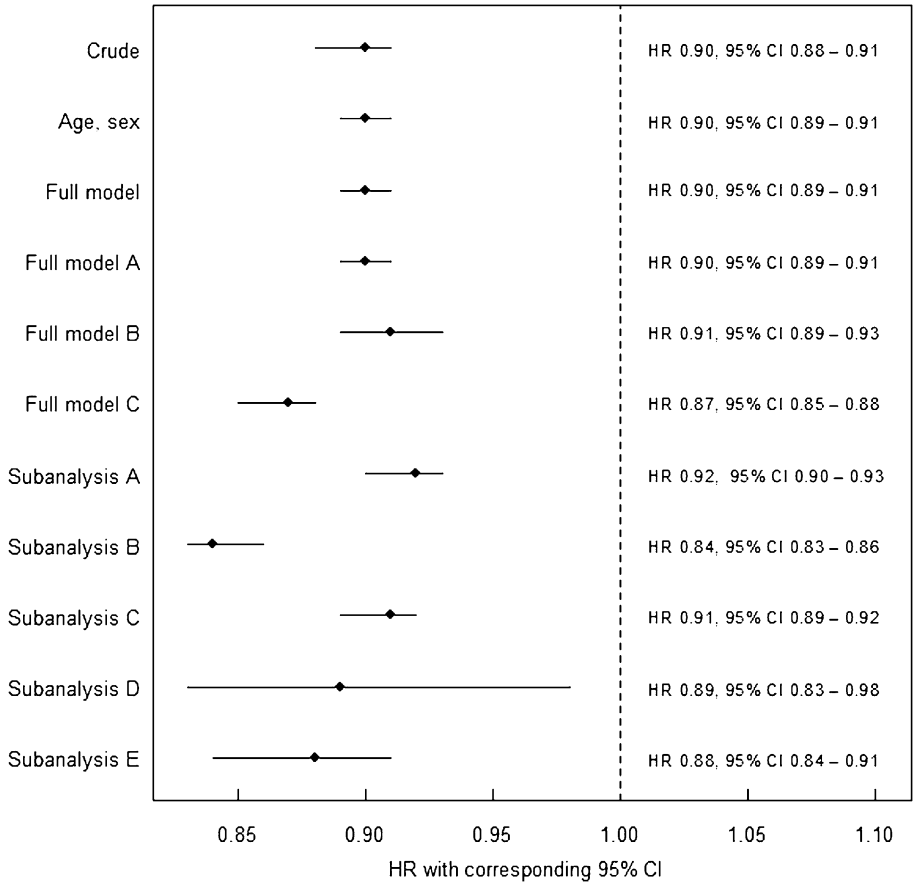

Figure 1—*Risk of cancer in patients when comparing cumulative exposure to metformin with cumulative exposure to sulfonylurea derivatives. The full model included the covariables age at first OGLD prescription, sex, calendar time (calendar year in which the first prescription was dispensed), hospitalizations (number of hospitalizations in the year before the start of the OGLD), and unique drugs (number of unique drugs dispensed in the year before the start of the OGLD). Full model A additionally included the average DDD, which was the dosage calculated over all previous OGLD prescriptions. Full model B was stratified for dosage of the first OGLD prescription lower than the median dosage. Full model C was stratified for dosage of the first OGLD prescription higher than the median dosage. Subanalysis A included a 1-year latency period, in which exposure was cumulated until 1 year before the date of the cancer diagnosis. Subanalysis B included only those with more than 1 year of exposure since the start of the OGLD. In subanalysis C, additional censoring took place at the moment metformin users started sulfonylurea and at the moment sulfonylurea users started metformin. Subanalysis D included only those treated with monotherapy metformin or sulfonylurea during the study period. Subanalysis E included only those who were treated with metformin as well as sulfonylurea derivatives during the study period (◆, HR; —, 95% CI).*

more than 365 days also resulted in lower estimates for all outcomes, with the exception of stomach cancer; this point estimate did not change.

Dosage-response relations could be identified for the use of metformin but not for the use of sulfonylurea derivatives. When those with an average DDD higher than the median were compared with those with an average DDD lower than the median, the crude HR was 0.80 (95% CI 0.72–0.89) for use of metformin. When applying the full model, the HR was 0.89 (0.80– 0.99) for use of metformin; however, for sulfonylurea derivatives, the crude HR was 1.00 (0.99–1.01), and when applying the full model, the HR was 1.00 (0.99–1.01).

CONCLUSIONS—In this study, we found that use of metformin was associated with a significantly lower risk of cancer in general and of specific cancers compared with the use of sulfonylurea derivatives. The HR of 0.90 (95% CI 0.88–0.91) found in our study is comparable to the odds ratio of 0.86 (0.73–1.02) with reference to no metformin use found by Evans et al. (4). However, they presented a subset of patients included in a study published later in which a lower HR for the use of metformin of 0.63 (0.53–0.75, adjusted) was described compared with no metformin use (6). In addition, in an Italian case–control study, exposure to metformin and gliclazide was associated with a reduction in the risk of cancer of 0.28 (0.13–0.57) compared with no exposure (8). Others found that use of metformin monotherapy compared with sulfonylurea derivative monotherapy was associated with a decreased risk of cancer of 0.74 (0.65–0.84) (5,15).

In our opinion, the differences in estimates can be largely explained by differences in the study populations, designs, methods of collecting risk factors and estimation of the exposure to metformin (duration and dosage), the comparators used, and the start of follow-up. The association with age in our study can be explained by the increased risk of cancer at an older age; the association with hospitalization before the start of OGLD might be explained by better screening and earlier diagnosis. Dosage-dependent relations could be demonstrated for metformin but not for sulfonylurea derivatives. We hypothesized that the differences in mean average DDD between those using metformin (0.7) and those using sulfonylurea derivatives (1.5) could be partly explained by a lower tolerability of participants to metformin compared with sulfonylurea derivatives.

Strengths and limitations

Because diabetes itself is associated with cancer, our study included only incident users of metformin or sulfonylurea derivatives, which was defined as a prescription-free period of 6 months before study entry (23). Follow-up started at the date of the first prescription of an OGLD; thus, adjustment for duration of diabetes in our study was optimal, and consequently, all participants had a more or less similar duration of diabetes mellitus. However, we were not able to filter out those who used metformin for other indications (e.g., polycystic ovarian disease). Such diseases occur at a low frequency, and these indications are not registered in the Netherlands. Consequently, the number of those using metformin for indications other than diabetes most likely was too low to bias the risk estimates in our study.

In addition, because this study included only those with diabetes who were treated with drugs, no comparison could be made with those who were treated with lifestyle changes. Furthermore, no information was available on cause of death,

Table 2—*Risk of specific cancers in patients when comparing cumulative exposure to metformin with cumulative exposure to sulfonylurea derivatives*

	Metformin		Sulfonylurea derivatives		HR of metformin with reference to sulfonylurea derivatives
Cancer	*n* *	IR†	*n* *	IR†	HR‡ (95% CI)
Esophagus	45	0.30	46	0.30	0.90 (0.82–0.97)
Stomach	47	0.32	70	0.46	0.83 (0.76–0.90)
Colon	228	1.53	299	1.97	0.91 (0.88–0.94)
HCC	16	0.11	15	0.10	0.67 (0.53–0.86)
Pancreas	60	0.40	106	0.70	0.73 (0.66–0.80)
Respiratory	203	1.36	251	1.66	0.87 (0.84–0.91)
Breast	207	2.63	217	2.81	0.95 (0.91–0.98)
Prostate	90	1.28	136	1.83	0.92 (0.88–0.97)

HCC, hepatocellular carcinoma. *Number of events. †IR, incidence rate/1,000 patient-years. ‡Hazard ratio applying the full model in which adjustments were made for age at first OGLD prescription, sex, year in which the first OGLD prescription was dispensed, number of unique drugs used in the year, and number of hospitalizations in the year before the start of the OGLD.

and we were not able to verify whether use of metformin was associated with a decreased risk of cancer death compared with sulfonylurea derivatives, as published earlier (24).

We were indirectly able to adjust for comorbidity because we had information on other drugs used and on the number of hospitalizations before the first prescription of OGLD. However, in contrast to some former studies, we were not able to adjust for smoking status or BMI, which might be considerable confounding factors. Similar to others, one of the most important issues that we could not address was the clinical decision-making process that determined each patient's treatment.

Reverse causality may play a role in observational studies because cancer often has a long latency period during which the disease is already present but has not yet been diagnosed. During this long latency period, the disease itself may cause changes in treatment and, therefore, the assessment of etiologically relevant timing of exposure is of pivotal importance (18). By taking into account a latent period, when disease is already present but not yet diagnosed, by cumulating exposure to 1 year before the date of diagnosis, we attempted to minimize reverse causality; this did not change the HR. Other sensitivity analyses to test the robustness of our results were performed as well, none of them changing the HR more than 10%.

PHARMO RLS is a population-based database; thus, selection bias is negligible because everybody using any prescription at any time is enrolled in certain geographic regions. Misclassification of exposure is unlikely because all information on dispensed prescriptions is gathered prospectively and automatically. Furthermore, misclassification of the outcome was unlikely because this was collected independently of the exposure of interest in our study. However, we used cancer hospitalization as an outcome measure, which is different from pathology data on cancer diagnoses. Some cancers might be diagnosed and treated more frequently on an outpatient basis. However, as cancers are coded independently of the exposure, within each specific cancer, this would lead to nondifferential misclassification of the outcome and consequently to dilution of the estimated effect toward the null-hypothesis.

Several possible biologic mechanisms that might explain the protective effect of metformin on the risk of cancer have been described (25); however, it should be emphasized that these are largely speculative. The decreased risk of cancer in those using metformin compared with those using sulfonylurea derivatives could also be explained as an increased risk of cancer in those using sulfonylurea derivatives compared with those using metformin. Because sulfonylurea derivatives increase the levels of endogenous insulin, this would be a plausible biologic underlying mechanism as well. In our opinion, this option seems less likely because results in the group treated with a combination of metformin and sulfonylurea derivatives were comparable to those on monotherapy with metformin. Despite this, it is premature to draw any conclusions from these two subanalyses.

In conclusion, cumulative exposure to metformin in our study was associated with a lower risk of cancer in general and of specific cancers compared with cumulative exposure to sulfonylurea derivatives. However, whether this should indeed be seen as a decreased risk of cancer for the use of metformin compared with the use of sulfonylurea derivatives or as an increased risk of cancer for the use sulfonylurea derivatives compared with the use of metformin remains to be elucidated.

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