Mortality After Incident Cancer in People With and Without Type 2 Diabetes

Impact of metformin on survival

Craig J. Currie, phd[1]
Chris D. Poole, phd[2]
Sara Jenkins-Jones, msc[2]
Edwin A.M. Gale, md[3]
Jeffrey A. Johnson, phd[4]
Christopher Ll. Morgan, msc[2]

OBJECTIVE—Type 2 diabetes is associated with an increased risk of several types of cancer and with reduced survival after cancer diagnosis. We examined the hypotheses that survival after a diagnosis of solid-tumor cancer is reduced in those with diabetes when compared with those without diabetes, and that treatment with metformin influences survival after cancer diagnosis.

RESEARCH DESIGN AND METHODS—Data were obtained from >350 U.K. primary care practices in a retrospective cohort study. All individuals with or without diabetes who developed a first tumor after January 1990 were identified and records were followed to December 2009. Diabetes was further stratified by treatment regimen. Cox proportional hazards models were used to compare all-cause mortality from all cancers and from specific cancers.

RESULTS—Of 112,408 eligible individuals, 8,392 (7.5%) had type 2 diabetes. Cancer mortality was increased in those with diabetes, compared with those without (hazard ratio 1.09 [95% CI 1.06–1.13]). Mortality was increased in those with breast (1.32 [1.17–1.49]) and prostate cancer (1.19 [1.08–1.31]) but decreased in lung cancer (0.84 [0.77–0.92]). When analyzed by diabetes therapy, mortality was increased relative to nondiabetes in those on monotherapy with sulfonylureas (1.13 [1.05–1.21]) or insulin (1.13 [1.01–1.27]) but reduced in those on metformin monotherapy (0.85 [0.78–0.93]).

CONCLUSIONS—This study confirmed that type 2 diabetes was associated with poorer prognosis after incident cancer, but that the association varied according to diabetes therapy and cancer site. Metformin was associated with survival benefit both in comparison with other treatments for diabetes and in comparison with a nondiabetic population.

Diabetes Care 35:299–304, 2012

Certain types of cancers are more common in people with diabetes than in those without (1–3), and diabetes is also associated with reduced survival after cancer (4,5). Interpretation of these observations is, however, confounded by the greater comorbidity and reduced life expectancy associated with diabetes, and by the possibility that those with diabetes may have less effective cancer screening (6–8), leading to delayed diagnosis. It is also possible that people with diabetes may respond less effectively to some cancer therapies, or that they may tolerate them less well.

Patients who take metformin for type 2 diabetes have a lower overall risk of cancer and lower cancer mortality than those on other glucose-lowering therapies (9–11). This finding has emerged consistently from both randomized and observational studies, and a number of mechanisms have been proposed by which metformin might suppress the growth of cancer cells, including reducing the concentration of circulating insulin, inducing apoptosis, and activating metabolic pathways such as LKB1/AMP-activated protein kinase (AMPK) (12). However, there are concerns about confounding by indication because metformin-treated patients have different clinical characteristics than other diabetes-related treatment groups, such as those treated with insulin. Metformin is now recommended as the first-line treatment for all patients with type 2 diabetes, and is also under consideration for use in nondiabetic patients as an adjunctive therapy for cancer. There is therefore an urgent need to understand its potential effect on cancer prognosis.

This study aimed to characterize patterns of survival after incident cancer in people with type 2 diabetes, compare these with survival patterns in the nondiabetic population, and, in particular, determine if postcancer survival was related to the type of medication used to treat diabetes.

RESEARCH DESIGN AND METHODS

Data and subjects

Anonymous, routine data compiled from >350 primary care practices in the U.K. were analyzed in a retrospective cohort study. Available data included patient demographics, medical history (including diagnoses and health contacts), biochemistry and microbiology test results, and pharmaceutical prescriptions. Ethnicity was recorded sparsely for general practice locality but not at all for individuals and is therefore not included in our study. Diagnostic information was recorded using the Read code classification, used throughout general practice in the U.K. (13).

Observational time periods

Subjects were selected from practices from 1990, or from the date of the practice's acceptable mortality ratio, whichever was later. The acceptable mortality ratio ensures that the mortality patterns reported by practices are as expected

From the [1]Department of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, U.K.; [2]Global Epidemiology, Pharmatelligence, Cardiff, U.K.; [3]Diabetes and Metabolism, School of Clinical Sciences, University of Bristol, Bristol, U.K.; and the [4]School of Public Health, University of Alberta, Edmonton, Alberta, Canada.
Corresponding author: Craig J. Currie, currie@cardiff.ac.uk.
Received 13 July 2011 and accepted 28 October 2011.
DOI: 10.2337/dc11-1313
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1313/-/DC1.

based on the application of national mortality statistics. This helps remove the potential bias from a survivor effect. The final observation was in December 2009.

A minimum wash-in period of 2 years from general practice registration to cancer diagnosis was used to ensure that the identified cancer was the first cancer occurrence. Subjects' records were followed over time and were censored due to death, departure from the general practice, or 31 December 2009, whichever occurred first.

Patient selection

Selection was based upon a first diagnosis of a solid tumor. Cancer diagnoses recorded in general practice routine data in the U.K. have been empirically validated and have a high positive predictive value (14). Diabetes was identified by a Read code indicative of diabetes and was flagged as type 1 or type 2 diabetes. Type 1 diabetes was subsequently excluded from all analyses. Individuals aged <35 years at cancer diagnosis and those with hematological cancers prior to the solid tumor were excluded.

In order to examine the impact of selected glucose-lowering therapies, subjects with type 2 diabetes were further subdivided by selected regimens at cancer diagnosis: metformin, sulfonylurea, and insulin monotherapy. Patients were classified into these monotherapy groups by their treatment in the 90 days before their cancer diagnosis. A sensitivity analysis considered only those people treated with these specific monotherapy regimens 90 days after cancer diagnosis. In all cases, monotherapy with glucose-lowering therapies was indicated by a time-fixed, binary covariate.

Data analysis

The primary outcome measure was all-cause mortality. The data lacked sufficient detail to capture cancer-specific mortality accurately. The analysis was first applied to all cancers and then replicated for cancer-specific sites: breast, prostate, colorectum, lung, bladder, ovary/endometrium, pancreas, and liver, selected because of their high frequency or their identification as a cancer of particular interest in the diabetic population.

Kaplan-Meier analysis was used to estimate mean and median survival. Cox proportional hazards models were used to account for differences in cohort characteristics. The reference group was the nondiabetic group for all analyses other than those limited to the diabetic population, where the reference group was metformin monotherapy. The specification of the baseline Cox model included three covariates: age, sex, and smoking status, before the addition of other covariates. Comorbidity was classified using the Charlson index (15), adapted in order to exclude diabetes and the index cancer as predictor variables. Additional covariates included year of cancer diagnosis, Townsend index of deprivation, HbA_{1c}, and the number of general practice contacts, which

Table 1—*Baseline characteristics of cohorts at cancer diagnosis*

			Type 2 diabetes treatment groups				
	Nondiabetes	Type 2 diabetes	Met mono	Sulf mono	Insulin mono	Met + Sulf	Met + insulin
Patients, *n* (%)	104,016	8,392	1,428 (17.0)	1,519 (18.1)	654 (7.8)	1,125 (13.4)	290 (3.5)
Follow-up, total (median), years	353,056 (2.0)	22,037 (1.6)	3,794 (1.8)	4,351 (1.6)	1,699 (1.5)	3,221 (1.9)	605 (1.3)
Age, mean (SD), years	67.5 (13.0)	71.7 (9.5)	70.4 (9.8)	74.1 (8.9)	70.4 (9.4)	71.9 (8.8)	67.8 (8.7)
Sex							
Male, *n* (%)	49,146 (47.2)	4,940 (58.9)	791 (55.4)	918 (60.4)	379 (58.0)	688 (61.2)	163 (56.2)
Female, *n* (%)	54,870 (52.8)	3,452 (41.1)	637 (44.6)	601 (39.6)	275 (42.0)	437 (38.8)	127 (43.8)
Smoking							
Current, *n* (%)	22,207 (21.3)	1,341 (16.0)	241 (16.9)	248 (16.3)	113 (17.3)	163 (14.5)	43 (14.8)
Ex, no. (%)	24,422 (23.5)	3,129 (37.3)	541 (37.9)	505 (33.2)	249 (38.1)	418 (37.2)	126 (43.4)
Diabetes duration, mean (SD), years	N/A	7.7 (7.0)	5.3 (5.5)	6.9 (5.9)	12.8 (8.6)	9.2 (6.7)	13.5 (7.4)
BMI, mean (SD), kg/m^2	25.9 (4.3)	29.4 (5.1)	30.7 (5.1)	27.7 (4.5)	28.9 (5.1)	29.4 (4.8)	31.6 (5.3)
Systolic BP, mean (SD), mmHg	139.6 (19.8)	138.6 (19.3)	137.8 (18.3)	140.7 (21.0)	139.4 (19.9)	138.9 (17.9)	137.9 (17.6)
Cholesterol, mean (SD), mmol/L	5.1 (1.2)	4.4 (1.1)	4.3 (1.1)	4.5 (1.2)	4.3 (1.1)	4.3 (1.1)	4.1 (1.0)
HbA_{1c}, mean (SD), %	N/A	7.4 (1.5)	7.1 (1.3)	7.4 (1.5)	8.4 (1.6)	7.7 (1.5)	8.3 (1.5)
Other morbidity							
Large vessel disease, *n* (%)	15,787 (15.2)	2,665 (31.8)	393 (27.5)	513 (33.8)	265 (40.5)	359 (31.9)	104 (35.9)
Renal disease, *n* (%)	964 (0.9)	628 (7.5)	87 (6.1)	127 (8.4)	75 (11.5)	75 (6.7)	22 (7.6)
Primary care contacts preceding year, mean (SD)	7.0 (6.9)	11.2 (9.5)	10.8 (9.0)	10.3 (9.1)	13.6 (11.7)	10.8 (8.8)	12.6 (9.6)
Charlson index, mean (SD)	2.5 (0.9)	4.2 (1.4)	3.9 (1.2)	4.2 (1.5)	4.9 (1.7)	4.2 (1.3)	4.5 (1.5)
Charlson index (age adjusted), mean (SD)	4.8 (1.8)	6.9 (1.8)	6.5 (1.7)	7.2 (1.9)	7.4 (2.0)	7.0 (1.7)	6.8 (1.8)
Charlson index (adjusted*), mean (SD)	0.5 (0.8)	0.8 (1.1)	0.6 (0.9)	0.9 (1.1)	1.1 (1.3)	0.8 (1.0)	0.8 (1.0)
Townsend index of deprivation, mean (SD)	2.7 (1.4)	2.9 (1.4)	2.9 (1.4)	2.9 (1.4)	2.9 (1.3)	2.8 (1.4)	2.9 (1.4)

Met, metformin; mono, monotherapy; Sulf, sulfonylurea. *Index adjusted to exclude diabetes and the index cancer.

was log transformed because of severe skewed distribution.

The threshold for statistical significance was set at the conventional level of $\alpha = 0.05$, and 95% CIs for hazard ratios (HRs) were calculated. Records with missing data were excluded automatically in the respective models. We tested the proportional hazards assumption for the Cox models by examining the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that progressed to an event (16).

RESULTS

Subjects and baseline characteristics

Data were available for 112,602 people with solid tumors. Of these, 194 (0.2%) had type 1 diabetes and were excluded. Of the remaining 112,408 subjects, 8,392 (7.5%) had type 2 diabetes. Table 1 shows the baseline characteristics by nondiabetes and diabetes and by subsets of glucose-lowering therapy at the time of cancer diagnosis.

Those with type 2 diabetes were older (71.7 years, SD 9.5, vs. 67.5 years, SD 13.0; $P < 0.001$), more likely to be male (58.9 vs. 47.2%; $P < 0.001$), and had greater baseline morbidity, whether measured in terms of vascular disease (31.8 vs. 15.2%; $P < 0.001$), prior general practice contacts (11.2 vs. 7.0%; $P < 0.001$), or the Charlson index after adjusting for age (6.9 vs. 4.8 units; $P < 0.001$), when compared with the nondiabetic group. Those with type 2 diabetes had a higher BMI (29.4 vs. 25.9 kg/m^2; $P < 0.001$), but other modifiable risk factors were more favorable; for example, the proportion of current smokers (16.0 vs. 21.3%; $P < 0.001$) and cholesterol (4.4 vs. 5.1 mmol/L; $P < 0.001$).

There were also differences in baseline characteristics between diabetes-related treatment regimens. For example, 40% of people treated with insulin-only regimens were found to have a record of large vessel disease at cancer diagnosis versus 27% of those treated with metformin monotherapy ($P < 0.001$) (Table 1).

Overall mortality

The median (SE) and mean (95% CI) for overall survival were 6.8 (0.08) and 9.3 years (9.2–9.4), respectively. There was a significant difference in the unadjusted, overall hazard of mortality in people with diabetes versus nondiabetes (HR 1.24 [95% CI 1.20–1.29]) (Supplementary Fig. 1*A*). After the inclusion of other

Table 2—*Unadjusted mean and median survival from time of cancer diagnosis and adjusted* relative mortality, by cancer site*

	No diabetes					Type 2 diabetes					Adjusted relative mortality	
Cancer site	Cases	Deaths	*n*/PKPY	Mean (95% CI), years	Median (SE), years	Cases	Deaths	*n*/PKPY	Mean (95% CI), years	Median (SE), years	HR (95% CI)	*P*
Overall	104,016	42,602	120.7	9.5 (9.4–9.5)	7.1 (0.9)	8,392	3,780	171.5	7.0 (6.7–7.3)	4.6 (0.1)	1.24 (1.20–1.29)	<0.001
Bladder	5,968	2,287	102.5	9.4 (9.1–9.7)	7.8 (0.3)	675	268	113.4	8.3 (7.5–9.1)	6.2 (0.4)	1.16 (1.02–1.32)	0.027
Breast	24,393	4,796	38.8	14.3 (14.1–14.4)	19.6 (0.4)	1,182	328	76.9	10.4 (9.5–11.3)	9.4 (0.8)	1.32 (1.17–1.49)	<0.001
Colorectal	13,388	5,742	136.8	8.6 (8.4–8.8)	5.5 (0.2)	1,285	532	147.5	7.3 (6.6–8)	5.1 (0.3)	1.00 (0.91–1.10)	0.992
Liver	1,217	876	742.0	2.4 (2.0–2.8)	0.5 (0.0)	243	163	661.0	2.4 (1.5–3.2)	0.7 (0.1)	0.88 (0.74–1.05)	0.157
Lung	11,611	8,916	870.9	1.8 (1.7–1.9)	0.5 (0.0)	856	595	689.2	2.2 (1.8–2.6)	0.7 (0.0)	0.84 (0.77–0.92)	<0.001
Ovary/endometrium	4,732	1,832	111.9	9.9 (9.6–10.3)	7.9 (0.5)	394	136	112.7	8.6 (7.3–9.8)	8.4 (0.9)	0.87 (0.72–1.04)	0.120
Pancreas	1,944	1,532	1,343.6	1.2 (1–1.4)	0.3 (0.0)	364	288	1,184.1	1.1 (0.8–1.3)	0.3 (0.0)	0.98 (0.86–1.12)	0.764
Prostate	15,256	4,894	89.3	9.1 (8.8–9.3)	7.9 (0.1)	1,385	465	105.5	7.5 (6.9–8.0)	6.7 (0.2)	1.19 (1.08–1.31)	0.001
Other	25,507	11,727	143.8	8.6 (8.4–8.7)	5.2 (0.2)	2,008	1,005	208.0	6.1 (5.6–6.5)	3.2 (0.3)	—	—

KPY, per thousand patient-years. *Cox model specification: age at baseline, sex, smoking history, Charlson comorbidity index, and year of diagnosis.

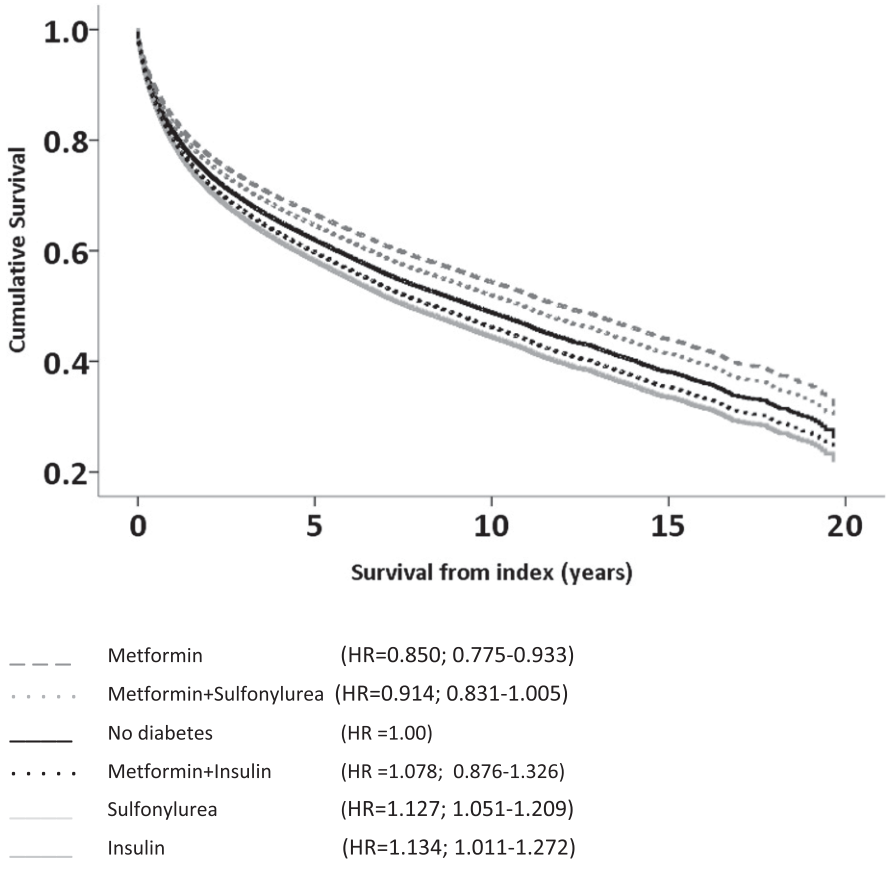

Figure 1—*Adjusted* survival using alternative diabetes-related treatment regimens: monotherapy within 90 days of cancer diagnosis. Note: the patterns of survival in the insulin and sulfonylurea groups are the same. *Cox model specification: age, sex, smoking status, year of cancer diagnosis, and Charlson comorbidity index.*

variables into the model (age at baseline, sex, smoking status, Charlson index, and year of cancer diagnosis), the HR remained significant at 1.10 (1.07–1.14) (Supplementary Fig. 1*F*). BMI was significant in the model, although it had no meaningful impact on the other HRs, but was excluded from the analysis because of missing data, which disproportionately affected the nondiabetic group. When the models were run with BMI included, there was no impact upon the HRs for diabetes versus nondiabetes.

Mortality by cancer site

Mortality differences by diabetes status varied considerably by cancer site (Table 2). For example, women with breast cancer had a mean survival time of 10.4 years if they had diabetes, versus 14.3 years if they did not. In lung cancer, however, mean survival times were 2.2 and 1.8 years, respectively. When adjusted using the Cox model (Table 2), diabetes was associated with significantly greater mortality in patients with breast (HR 1.32 [1.17–1.49]) or prostate cancer (HR 1.19 [1.08–1.31]) compared with those without diabetes. Conversely, diabetes was associated with improved lung cancer survival compared with those without diabetes (HR 0.84 [0.77–0.92]).

Mortality by glucose-lowering therapy

People with diabetes receiving metformin monotherapy for 90 days before cancer diagnosis had significantly reduced overall mortality (HR 0.85 [0.78–0.93]), compared with those without diabetes (Fig. 1). In contrast, those treated with sulfonylurea monotherapy (1.13 [1.05–1.21]) or insulin alone (1.13 [1.01–1.27]) had increased mortality. For combination therapy, there was no significant association with mortality: metformin and insulin (1.08 [0.88–1.33]) and metformin and sulfonylurea (0.91 [0.83–1.01]).

When comparing different monotherapies in patients with diabetes, those receiving sulfonylurea monotherapy (HR 1.48 [1.29–1.71]) or insulin alone (1.33 [1.18–1.58]) had significantly increased mortality relative to metformin monotherapy. The combination therapies metformin and sulfonylurea (1.09 [0.94–1.27]) and insulin and metformin (1.28 [0.96–1.64]) were not significant.

In site-specific analysis, reduced mortality was observed in subjects treated with metformin monotherapy at the time of diagnosis for liver (HR 0.47 [0.24–0.91]) and ovarian/endometrial cancer (0.48 [0.28–0.81]), although no mortality differences were noted for the other cancer sites (Table 3). In sensitivity analysis considering patients treated with monotherapy for 90 days after a cancer diagnosis, significant differences were noted for lung (0.77 [0.59–1.00]) and ovarian/endometrial cancer (0.42 [0.23–0.77]).

CONCLUSIONS—We set out to determine whether a diagnosis of solid-tumor cancer was associated with shorter survival in people with type 2 diabetes when compared with those without diabetes, and whether metformin influenced this. The study confirmed that survival was reduced in those with diabetes after a diagnosis of cancer. After controlling for confounding factors, type 2 diabetes was associated with an ~10% increase in mortality for all cancers in comparison with those who did not have diabetes. This observation should, however, be considered with some caution because the increased mortality may have been related to the diabetes rather than to the cancer. When prognosis was examined by cancer type, bladder, breast, and prostate cancers were associated with diminished survival. The increased mortality for breast cancer confirms previous data reporting a significant HR of 1.4 for those with diabetes versus those without (11). Here, however, diabetes was associated with slightly longer survival from lung cancer (1.8 vs. 2.2 years).

The study also showed that metformin therapy in the period preceding diagnosis was associated with a better prognosis after a diagnosis of cancer, compared not only with other forms of diabetes therapy but also with the nondiabetic population.

Although these data need cautious interpretation, they suggest that exposure to metformin after diagnosis is associated with improved survival for the majority of sites,

Table 3—*Adjusted* survival by cancer site in people exposed versus not exposed to metformin immediately before and after cancer diagnosis*

	±Metformin (immediately before cancer diagnosis)				±Metformin (≤3 months after cancer diagnosis)			
Cancer site	Cases	Deaths	HR (95% CI)	*P*	Cases	Deaths	HR (95% CI)	*P*
All cancer	112,408	46,382	0.899 (0.814–0.993)	0.036	94,363	33,444	0.903 (0.815–1.001)	0.054
Bladder	6,643	2,555	0.888 (0.556–1.417)	0.619	5,954	2,114	0.958 (0.643–1.426)	0.834
Breast	25,575	5,124	0.963 (0.675–1.373)	0.836	24,186	4,671	0.967 (0.695–1.345)	0.846
Colorectum	14,673	6,274	0.889 (0.666–1.187)	0.427	12,443	4,733	0.881 (0.669–1.161)	0.370
Liver	1,460	1,039	0.467 (0.241–0.906)	0.024	819	514	0.932 (0.507–1.715)	0.823
Lung	12,467	9,511	0.834 (0.665–1.045)	0.115	7,345	5,204	0.767 (0.590–0.997)	0.048
Ovary/endometrium	5,863	2,223	0.480 (0.283–0.814)	0.007	5,021	1,661	0.423 (0.233–0.767)	0.005
Pancreas	2,308	1,820	1.256 (0.853–1.849)	0.247	1,142	841	0.652 (0.381–1.114)	0.118
Prostate	16,641	5,359	1.266 (0.967–1.658)	0.086	15,480	4,819	1.232 (0.967–1.571)	0.091
Other cancers	26,778	12,477	0.894 (0.747–1.070)	0.224	21,973	8,887	0.889 (0.727–1.087)	0.252

*Cox model specification: age, sex, smoking history, Townsend index of deprivation, Charlson comorbidity index, number of primary care contacts (log transformed), and year of diagnosis.

although this was only statistically significant for cancers of the ovary/endometrium and the lung. Interestingly, this list did not include breast cancer, for which metformin is being studied in controlled trials as an anticancer agent. These findings add to the evidence that metformin may be of benefit in the prevention and/or treatment of some, but potentially not all, types of cancer. However when used in combination with either sulfonylurea or insulin, there was no significant difference in HR.

The difference in hazard between those with diabetes and those without was lower in our study than has, to our knowledge, been reported previously. For example, van de Poll-Franse et al. (17) reported an HR of 1.4, a value that was replicated almost exactly in a related meta-analysis by Barone et al. (5). This may in part be due to the additional covariates used in our analysis, but these differences do warrant further investigation.

This study had both strengths and limitations. The most obvious strength was the large number of cancer and mortality events in the overall analysis. These data from general clinical practice may be considered representative of the general population, and the considerable detail of the drug exposure data was also a major advantage. Analysis of drug exposure is, however, complicated by changes in therapy, and we avoided this problem by restricting the analysis to those who remained on monotherapy before or after a diagnosis of cancer. In consequence, our analysis was restricted to those on monotherapy with metformin, insulin, and sulfonylureas or to those treated with metformin in combination with either sulfonylureas or insulin, representing ~60% of the overall diabetic population. This creates some difficulty in interpretation. For example, the observation that those on metformin alone preceding a diagnosis of cancer had a better prognosis might indicate that these individuals were healthier or better able to resist cancer than those on other therapies. Equally, however, it might simply mean that they were more likely to have remained on long-term metformin therapy after a diagnosis of cancer. Confounding by indication may also, and for similar reasons, be a concern when it comes to the observed lack of survival benefit for those allocated to sulfonylureas or insulin.

Other limitations include the lack of statistical power within some of the low-incidence cancers; thus, we restricted ourselves to analysis of metformin exposure as a simple binary variable. We did not have reliable data on cancer staging at diagnosis. Patients with and without diabetes may therefore have been diagnosed at different stages of the condition. We also did not have detailed information on cancer treatments received, which may have differed between those with and without diabetes. Furthermore, we did not have reliable data on cause of death and therefore relied on all-cause mortality as the outcome measure. Patients may therefore have died of causes other than cancer, and overall mortality will clearly be greater for patients with diabetes due to associated vascular causes. This may be particularly pertinent for tumors with a long survival period.

In summary, this analysis confirms that patients with diabetes who are diagnosed with cancer have a shorter survival relative to nondiabetes, but this relatively small (10%) overall difference may reflect reduced survival due to diabetes rather than a worse outcome from the cancer. We also observed a reduced mortality in diabetic patients treated with metformin monotherapy whether before or after cancer diagnosis, as compared with those on other forms of therapy for diabetes. The most striking observation was that diabetic patients treated with metformin had lower mortality than that of the background population, raising the possibility that metformin might come to play a wider role in cancer prevention and therapy.

Acknowledgments—This study was funded in part by the European Foundation for the Study of Diabetes. J.A.J. is a Senior Scholar with Alberta Innovates-Health Solutions and holds a Canada Research Chair in Diabetes Health Outcomes. C.J.C. has received research grants from various health-related organizations, including Astellas, Diabetes UK, the European Association for the Study of Diabetes, the Engineering and Physical Sciences Research Council, Ferring, GlaxoSmithKline (GSK), Lilly, Medtronic, the Medical Research Council, Merck, Pfizer, sanofi-aventis, and the National Health Service, and consults for Amylin, Aryx, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Diabetes UK, Eisel, Ferring, GSK, Ipsen, Lilly, Medtronic, Merck, Pfizer, sanofi-aventis, and Takeda. C.D.P. consults for Astellas, Ferring, Lilly, Medtronic, Novo Nordisk, sanofi-aventis, and Wyeth (Pfizer). S.J.-J. and C.Ll.M. are employed by a research consultancy receiving funding from pharmaceutical companies. No other potential conflicts of interest relevant to this article were reported.

C.J.C. contributed to discussion and wrote, reviewed, and edited the manuscript. C.D.P. researched data and wrote the manuscript. S.J.-J. researched data and reviewed and edited

the manuscript. E.A.M.G. and J.A.J. reviewed and edited the manuscript. C.Ll.M. researched data, contributed to discussion, and wrote the manuscript. C.Ll.M. 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.

References

1. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123
2. Nicolucci A. Epidemiological aspects of neoplasms in diabetes. Acta Diabetol 2010;47:87–95
3. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685
4. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat 2008; 109:389–395
5. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754–2764
6. Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. Arch Intern Med 2005;165:2090–2095
7. Maruthur NM, Bolen SD, Brancati FL, Clark JM. The association of obesity and cervical cancer screening: a systematic review and meta-analysis. Obesity (Silver Spring) 2009;17:375–381
8. Maruthur NM, Bolen S, Brancati FL, Clark JM. Obesity and mammography: a systematic review and meta-analysis. J Gen Intern Med 2009;24:665–677
9. Evans JMM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304–1305
10. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JMM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 2009; 32:1620–1625
11. Currie CJ, Poole CD, Gale EAM. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–1777
12. Kourelis TV, Siegel RD. Metformin and cancer: new applications for an old drug. Med Oncol. 8 February 2011 [Epub ahead of print]
13. NHS Connecting for Health. Read codes [Internet]. Available from http://www.connectingforhealth.nhs.uk/systemsandservices/data/readcodes. Accessed 4 May 2011
14. Zhang H, Hammad TA, Giovannuci E, Kang E, Christiani DC. Validation of cancer diagnoses recorded in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2010;19(Suppl. 1):S1–S347
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383
16. Kleinbaum DG, Klein M. *Survival Analysis: A Self-Learning Text*. 2nd ed. New York, NY, Springer, 2005.
17. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JWW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer 2007;120:1986–1992