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

Impact of metformin on survival

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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.

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.

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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, HbA1c, and the number of general practice contacts, which

Table 1—Baseline characteristics of cohorts at cancer diagnosis

|                                | Nondiabetes | Type 2 diabetes | Type 2 diabetes treatment groups |
|--------------------------------|-------------|-----------------|---------------------------------|
|                                |             |                 | 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 (35.4) | 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/m²           | 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)    |
| HbA1c, 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 (1.3)    |
| Other morbidity                |             |                 |          |          |            |            |              |
| Large vessel disease, n (%)    | 15,787 (15.2) | 2,665 (31.8) | 393 (27.5) | 513 (33.8) | 265 (40.5) | 399 (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. 1A). After the inclusion of other
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. 1F). 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 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

| 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  | 2,355  | 0.888 (0.556–1.417) | 0.619 | 5,954  | 2,114  | 0.958 (0.643–1.426) | 0.834 |
| Breast                    | 25,375 | 5,124  | 0.963 (0.679–1.373) | 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.

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

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