Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

Clinical Cancer Research

Cancer Therapy: Clinical

See commentary by Pollak, p. 2723

Metformin Use Is Associated with Better Survival of Diabetic Patients with Pancreatic Cancer

Navid Sadeghi[1], James L. Abbruzzese[2], Sai-Ching J. Yeung[3], Manal Hassan[2], and Donghui Li[2]

Abstract

Purpose: Accumulating evidence suggests that metformin has antitumor activity. The aim of this study was to determine whether metformin use has a survival benefit in patients with pancreatic cancer.

Experimental Design: We conducted a retrospective study of patients with diabetes and pancreatic cancer treated at The University of Texas MD Anderson Cancer Center (Houston, TX). Information on diabetes history, including treatment modalities and clinical outcome of pancreatic cancer, was collected using personal interviews and medical record review. Survival analysis was carried out using a Kaplan–Meier plot, log-rank test, and Cox proportional hazards regression models.

Results: Among the 302 patients identified, there were no significant differences in demographic or major clinical characteristics between the patients who had received metformin ($n = 117$) and those who had not ($n = 185$). The 2-year survival rate was 30.1% for the metformin group and 15.4% for the non-metformin group ($P = 0.004$; χ^2 test). The median overall survival time was 15.2 months for the metformin group, and 11.1 months for the non-metformin group ($P = 0.004$, log-rank test). Metformin users had a 32% lower risk of death; the HR (95% confidence interval) was 0.68 (0.52–0.89) in a univariate model ($P = 0.004$), 0.64 (0.48–0.86) after adjusting for other clinical predictors ($P = 0.003$), and 0.62 (0.44–0.87) after excluding insulin users ($P = 0.006$). Metformin use was significantly associated with longer survival in patients with nonmetastatic disease only.

Conclusions: Our finding that metformin use was associated with improved outcome of patients with diabetes and pancreatic cancer should be confirmed in independent studies. Future research should prospectively evaluate metformin as a supplemental therapy in this population. *Clin Cancer Res; 18(10); 2905–12. ©2012 AACR.*

Introduction

Pancreatic cancer is the tenth most common cancer and the fourth most common cause of cancer death in the United States (1, 2). Despite advances in molecular biology and targeted cancer treatment, the prognosis for patients with pancreatic cancer remains extremely poor, with a 1-year survival rate of 24% and a 5-year survival rate of 6% (3). Novel strategies for the primary prevention, early detection, and effective treatment of this deadly disease are urgently needed.

Long-term type II diabetes mellitus has been associated with increased risk for pancreatic cancer (4, 5). As a potentially modifiable risk factor, weight control, dietary modification, and antidiabetic therapy may all influence the risk of diabetes-associated pancreatic cancer. Recent epidemiologic investigations conducted in cohorts of patients with diabetes (6–11) and patients with cancer (12–15) showed that the use of metformin, a common antidiabetic drug, was associated with lower risk of cancer or lower cancer mortality compared with the use of insulin or insulin secretagogues. Of particular interest, a retrospective cohort study of patients with diabetes (7) and a case–control study of pancreatic cancer (12) independently reported a 60% to 70% lower risk of pancreatic cancer in metformin users than in insulin or sulfonylurea users.

Data from 2 clinical studies also suggest that metformin use may have clinical benefits for patients with diabetes and cancer. A retrospective study of patients with breast cancer who received chemotherapy for early-stage disease found that the complete pathologic response rate of patients with diabetes receiving metformin ($n = 68$) was 3 times higher than that of patients with diabetes not receiving metformin ($n = 87$; ref. 16). Another retrospective study in 233 patients with diabetes and prostate cancer showed that the risk of death was 45% lower for metformin users (17). These observations have inspired much clinical interest in a

Authors' Affiliations: [1]The University of Texas School of Public Health; and Departments of [2]Gastrointestinal Medical Oncology and [3]Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, Texas

Note: Current address for N. Sadeghi: University of Texas Southwestern Simmons Cancer Center, Dallas, TX 75390.

Corresponding Author: Donghui Li, Department of Gastrointestinal Medical Oncology, Unit 426, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Phone: 713-834-6690; Fax: 713-834-6153; E-mail: dli@mdanderson.org

doi: 10.1158/1078-0432.CCR-11-2994

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

Translational Relevance

Patients with pancreatic cancer often have a high prevalence (80%) of concurrent diabetes or impaired glucose tolerance, which are characterized by peripheral insulin resistance. Accumulating epidemiologic and experimental evidence suggest metformin, the most commonly used antidiabetic drug, as an antitumor agent. In this retrospective study of 302 patients with diabetes and pancreatic cancer, we observed that metformin users had 4 months longer overall survival time, 32% reduced risk of death, and about 2-fold higher 2-year survival rate than the non-metformin group. These observations add supporting evidence for the antitumor activity of metformin. Findings from this retrospective investigation should prompt future research to test the hypothesis that metformin can be used as a supplemental therapy in the treatment of pancreatic cancer.

potential role for metformin in the treatment of human cancers (18–20).

To examine whether metformin use has any survival benefits for patients with diabetes and pancreatic cancer, we conducted a retrospective study in a large cohort of patients with diabetes and pancreatic cancer. In this report, we show that metformin was an independent predictor of improved outcome in this population.

Materials and Methods

Study population

This retrospective cohort study included patients with pathologically confirmed pancreatic adenocarcinoma and precancer diagnoses of diabetes mellitus. All patients were identified from a case–control study of pancreatic cancer conducted at The University of Texas MD Anderson Cancer Center (Houston, TX) from January 2000 to May 2009. The study design and patient population for the case–control study have previously been described in detail (12). Cases were consecutively recruited from patients with newly diagnosed and pathologically confirmed pancreatic ductal adenocarcinoma who were presented at the MD Anderson Gastrointestinal Cancer Center. Patients who had a prior or concurrent malignancy were not included in the original study. For the current study, patients who were not treated at MD Anderson for pancreatic cancer were excluded because of the lack of follow-up information. We also excluded patients who did not have diabetes and patients who were recruited after June 2009 to ensure at least 1 year of follow-up for all patients. Each patient signed an informed consent and the study was approved by the Institutional Review Board at MD Anderson.

Data collection

In the original study, trained personnel administered a structured and validated questionnaire to collect information on demographics and known or suspected risk factors for pancreatic cancer (21). Body mass index (BMI) was calculated from self-reported weight and height. Preexisting diabetes mellitus was self-reported in patients' medical history and confirmed using the patients' medical records. Diabetes was defined as individuals with a self-reported history of diabetes or use of antidiabetic medications. Diabetes-related information included age and year of diagnosis, insulin administration and the duration of use, use of oral hypoglycemic medications (yes or no), names of the oral antidiabetic medications (metformin, sulfonylurea, or thiazolidinedione), and the duration of their use. Because the detailed medication history was not included in the questionnaire used before 2004, information on antidiabetic therapy used at the initial evaluation of their pancreatic cancer at MD Anderson was obtained via medical record review for 73 (24%) patients. In some of these cases, duration of use or prior history of medications was not available. For all patients, clinical information was collected via medical record review using an established abstraction form. Clinical variables collected included the date of pathologic diagnosis of pancreatic cancer, clinical tumor stage (i.e., resectable, locally advanced/unresectable, metastatic), primary tumor size, primary tumor site (i.e., head, body, or tail of the pancreas), serum CA-19-9 levels at diagnosis, treatment (i.e., chemotherapy, radiotherapy, and/or surgery), Eastern Cooperative Oncology Group (ECOG) performance status (0–3), and date of death or last follow-up.

Statistical analysis

Most patients with diabetes require more than one hypoglycemic agent to control their blood sugar, so the number of patients treated with monotherapy was very small. To ensure adequate study power, we compared patients who had ever received metformin and those who had never received metformin, regardless of the dose and duration of metformin use and other combinational therapies they had received. Overall survival (OS) time was calculated from the date of diagnosis to the date of death. Living patients were censored at the time of data analysis. Data were analyzed using Stata/IC 10.0 for Windows (StataCorp). Descriptive analysis included the distribution of pertinent variables (e.g., age, gender, BMI) in each group (metformin vs. non-metformin). Basic characteristics of the study population were compared between the 2 groups using Student t test for continuous variables and Pearson χ^2 test for categorical variables. A Kaplan–Meier plot was used to estimate the overall survival curves. Survival curves of the 2 groups were compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to evaluate potential predictors of survival. Variables showing significant associations with survival in univariate models were included in the multivariate model. In all instances, $P < 0.05$ was considered statistically significant.

Results

A total of 302 patients met the study criteria. The mean age of patients at cancer diagnosis was 64.0 ± 8.7 years (range, 37–84 years). Majority of the patients were men (65.6%) and non-Hispanic white (78.5%). Obesity, defined as BMI > 30 kg/m^2,

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

was noted in 18.2% of patients. The average BMI in the study population was 27.1 ± 5.4 kg/m^2, and there was no significant difference in average BMI between the metformin group (26.8 ± 5.1 kg/m^2) and the non-metformin group (27.4 ± 5.7 kg/m^2; $P = 0.531$). At the time of cancer diagnosis, 39.1% of patients had used insulin and 22.8% had undergone insulin monotherapy; 38.7% had used metformin and 15.6% had undergone metformin monotherapy; and 6.7% had never used any antidiabetic medications. Of the 302 patients examined, 240 (80%) had died as of May 2011. Twenty-two percent of the patients had resectable tumors, 41% had locally advanced disease, and 37% had metastatic disease. Other detailed clinical characteristics are described in Table 1. There were no significant differences between the

Table 1. Descriptive statistics of the patient population and subgroups

Variable	All patients, *n* (%)	Metformin, *n* (%)	Non-metformin, *n* (%)	*P*
Age, y				0.655
≤60	94 (31.1)	35 (29.9)	59 (31.9)	
61–70	139 (46.0)	52 (44.4)	87 (47.0)	
>70	69 (22.8)	30 (25.6)	39 (21.1)	
Sex				
Male	198 (65.6)	75 (64.1)	123 (66.5)	0.671
Race/ethnicity				0.076
White	237 (78.5)	96 (82.0)	141 (76.2)	
Black	25 (8.3)	8 (6.8)	17 (9.2)	
Hispanic	33 (10.9)	8 (6.8)	25 (13.5)	
Other	7 (2.3)	5 (4.3)	2 (1.1)	
BMI, kg/m^2				
≤25	114 (38.0)	46 (39.3)	68 (37.2)	0.911
25.1—30	124 (41.3)	48 (41.0)	76 (41.5)	
>30	62 (20.7)	23 (19.7)	39 (21.3)	
Diabetes duration, y				0.713
0–2	148 (49.0)	54 (46.2)	94 (50.8)	
>2—5	55 (18.2)	24 (20.5)	31 (16.8)	
>5—10	39 (12.9)	17 (14.5)	22 (11.9)	
>10	60 (19.9)	22 (18.8)	38 (20.5)	
Antidiabetics (ever used)				
Insulin	118 (39.1)	29 (24.8)	89 (48.1)	<0.001
Sulfonylurea	109 (36.1)	44 (37.6)	65 (35.1)	0.663
Metformin	117 (38.7)	117 (100)	0	
Thiazolidinedione	61 (20.2)	24 (20.5)	37 (20.0)	0.914
Tumor size,[a] cm	3.9 ± 1.6	4.0 ± 1.8	3.9 ± 1.5	0.412
Tumor site				
Tail involved	46 (15.2)	24 (20.5)	22 (11.9)	0.042
Stage				0.763
Resectable	67 (22.2)	27 (23.1)	40 (21.6)	
Unresectable	124 (41.1)	50 (42.7)	74 (40.0)	
Metastatic	111 (36.7)	40 (34.2)	71 (38.4)	
CA-19-9, U/mL				0.790
0–47	48 (16.0)	19 (16.4)	29 (15.8)	
>47–1,000	144 (48.0)	58 (50.0)	86 (46.7)	
>1,000	108 (34.0)	39 (33.6)	69 (37.5)	
Performance status				
0	42 (14.0)	18 (15.4)	24 (13.0)	
1	205 (68.1)	80 (68.4)	125 (67.9)	
2	42 (14.0)	13 (11.1)	29 (15.8)	0.569
3	12 (4.0)	6 (5.1)	6 (3.3)	

NOTE: Information about the following was missing: diabetes duration in 1 patient, BMI in 2 patients, CA-19-9 in 2 patients, tumor size in 23 patients, and performance status in 1 patient.

[a]Numbers are mean ± SD.

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

metformin group and non-metformin group in terms of age, sex, race, BMI, diabetes duration (from date of diabetes diagnosis to date of recruitment to the case–control study), disease stage, tumor size, performance status, and serum CA-19-9 level (Table 1). The metformin group had a lower prevalence of insulin use ($P < 0.001$) and a higher frequency of tumors of the pancreas tail ($P = 0.042$) than in the non-metformin group.

The median follow-up time was 11.4 months. The overall 1-year survival rate was 53.0% for all disease stages combined, 63.9% for the metformin group and 46.3% for the non-metformin group ($P = 0.002$; χ^2 test). The overall 2-year survival rate was 21.0% for all patients, 30.1% for the metformin group and 15.4% for the non-metformin group ($P = 0.004$; χ^2 test). The median OS time for all disease stages combined was 12.8 months [95% confidence interval (CI), 11.0–14.7]. Patients with locally advanced or metastatic disease had significantly shorter OS times than those with resectable tumors (Table 2). The median OS time was 4.1 months longer in the metformin group than in the non-metformin group ($P = 0.009$; log-rank test). Interestingly, the median OS time was longer in the metformin group than in the non-metformin group in each of the strata by disease stage (Table 2 and Fig. 1). However, the difference in survival between the metformin and non-metformin groups was statistically significant only in the patients with nonmetastatic disease ($P = 0.005$ for patients with nonmetastatic disease and $P = 0.482$ for patients with metastatic disease; log-rank test).

Univariate Cox proportional hazards regression analysis showed that disease stage, serum CA-19-9 level, tumor size, tumor site, performance status, and metformin use were significant predictors of OS in this study population (Table 3). Neither the use of insulin, sulfonylurea, or thiazolidinedione nor the administration of chemotherapy or radiotherapy had a significant impact on survival (data not shown). The HR and 95% CI were 1.04 (0.80–1.34), 0.91 (0.70–1.19), and 1.27 (0.93–1.74) for patients who had used insulin, sulfonylurea, and thiazolidinedione, respectively. Metformin use was associated with a 32% decrease in the risk of death (HR, 0.68; 95% CI, 0.52–0.89; $P = 0.004$). The metformin benefit remained significant after adjusting for other predictors in multivariate analysis (HR, 0.64; 95% CI, 0.48–0.86; $P = 0.003$) and after excluding insulin users (HR, 0.62; 95% CI, 0.44–0.87; $P = 0.006$). The HR (95% CI) for insulin alone were 1.01 (0.77–1.33) and 1.05 (0.78–1.41) in univariate and multivariate models, respectively. Among insulin users, the multivariate HR (95% CI) was 0.61 (0.32–1.16) for those who used metformin ($P = 0.13$). Because metastatic disease was more common in larger tumors and tumors of the pancreatic tail, these 2 predictors became nonsignificant in the multivariate model (Table 3). For patients with nonmetastatic disease in the metformin group, the HR (95% CI) was 0.53 (0.36–0.78) after adjusting for disease stage, tumor site, tumor size, performance status, and serum CA-19-9 level ($P = 0.001$).

The duration of metformin use in relation to overall survival was examined in 89 patients with available information. A weak beneficial effect on survival was observed for metformin use of 2 to 5 years compared with metformin use of less than 2 years (Table 4). However, long-term metformin use (>5 years) did not show further improvement on survival than the intermediate use (2–5 years).

Discussion

In this retrospective study of patients with pancreatic cancer and preexisting diabetes, we observed that the OS duration was 4.1 months longer and the 1-year survival rate was 18.8% higher in patients treated with metformin than in those not treated with metformin. The beneficial effect of metformin was seen in all disease stages but was statistically significant only in patients with nonmetastatic disease. Metformin use was associated with a 32% reduction in the risk of death, and the association remained statistically significant after adjusting for other clinical predictors and after excluding insulin users. These data provide strong supporting evidence that metformin has the potential to be used as a supplemental therapeutic agent for nonmetastatic pancreatic cancer.

Diabetes and pancreatic cancer have a complex, intertwined relationship. Long-term type II diabetes is a risk factor for pancreatic cancer. On the other hand, patients with pancreatic cancer are often subsequently diagnosed with diabetes or have impaired glucose tolerance. Although

Table 2. Median survival in months (95% CI) for patients with different stages of disease by metformin use

	All patients (N = 302)	Metformin (N = 117)	Non-metformin (N = 185)	*P*
All patients	12.8 (11.0–14.7)	15.2 (12.6–17.8)	11.1 (8.9–13.3)	0.009
Stage				
Resectable	28.2 (19.7–36.8)	31.0 (15.2–46.8)	21.4 (14.4–28.3)	0.293
Unresectable	13.8 (11.2–16.5)	15.5 (13.4–17.7)	11.0 (8.7–13.3)	0.001
Metastatic	8.3 (6.9–9.7)	8.8 (7.0–10.6)	7.3 (5.5–9.1)	0.482
Nonmetastatic[a]	16.6 (14.3–18.9)	20.8 (15.7–26.0)	14.8 (12.5–17.2)	0.005

[a]Combined group of patients with resectable and unresectable disease.

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

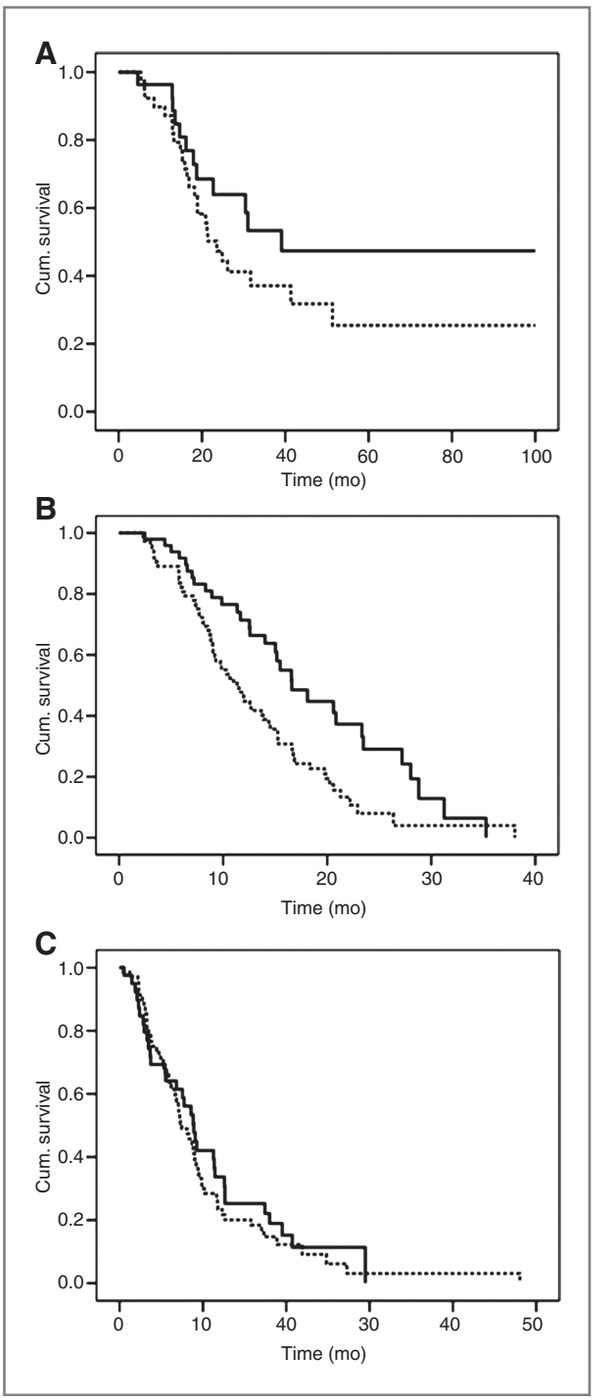

Figure 1. Survival curves (cum. survival) for the metformin group (solid line) and non-metformin group (dotted line) in patients with resectable (A), unresectable (B), and metastatic (C) pancreatic cancer. *P* values (log-rank test) were 0.293, 0.001, and 0.482 for A, B, and C, respectively.

the mechanism of pancreatic cancer–induced diabetes is not yet understood (22), insulin resistance and inflammation are the biologic mechanisms most frequently shared by diabetes and pancreatic cancer. The better clinical outcomes of patients in our study who used metformin could be related to lower circulating levels of insulin as a consequence of reduced insulin resistance. Insulin as well as insulin-like growth factor signaling play a key role in promoting cancer development (23). Furthermore, there is accumulating experimental evidence on a direct antitumor activity for metformin. Studies conducted in various animal tumor models (24–27) and cancer cell lines (28–32) have shown that metformin prevents tumor development and inhibits the growth of cancer cells. In pancreatic cancer, metformin has been shown to inhibit the growth of human cancer cells xenografted into nude mice via a mechanism of disrupted cross-talk between insulin receptor and G-protein–coupled receptor (31, 33). In a high-fat diet and carcinogen-induced pancreatic tumor model, metformin reduced the circulating level of insulin and completely prevented the development of tumors (34). The metabolic regulation and antitumor activity of metformin were mainly mediated through the activation of the liver kinase B1 (LKB1)-5′ AMP-activated protein kinase (AMPK) signaling pathway. Metformin reduces mitochondrial ATP production by inhibiting complex I of oxidative phosphorylation (35), which results in the activation of the LKB1-AMPK signaling pathway and in turn downregulates the AKT/mTOR pathway. AMPK is not only an energy homeostasis regulator but also acts as a metabolic checkpoint, coordinating cell growth with energy status to ensure the initiation and maintenance of cell polarity and the completion of normal cell division (36). Some studies also found that metformin could directly inhibit the mTOR pathway independent of AMPK activation (37, 38). Interestingly, metformin has been reported to selectively target the cancer stem cells and enhance the efficacy of chemotherapeutic drug in block tumor growth (39). Metformin may also exert its antitumor activity via regulating lipid metabolism, endothelial function, and immune functions (40–42). In our previously reported case–control study of pancreatic cancer, we showed that even a short duration (2 years) of metformin use was associated with reduced risk of pancreatic cancer (12), which suggests that metformin may not only prevent tumor development by inhibiting cell transformation and proliferation during the early stages of tumorigenesis but also may delay cancer progression (43). Findings from the current analysis are consistent with our previous observations, which support the notion that metformin could be used as a supplemental therapeutic agent for cancer. Considering the high prevalence of diabetes in patients with pancreatic cancer and the lack of effective treatment strategies for this malignancy, prospective studies should be conducted quickly to confirm the survival benefit of metformin use in patients with diabetes and pancreatic cancer.

The strengths of our study are the large sample size of patients with diabetes and pancreatic cancer and the detailed clinical information analyzed. The limitations of the study are its retrospective design and the associated recall bias and information bias. Although information on antidiabetic therapy was collected via personal interview in

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

Table 3. HRs and 95% CIs from univariate and multivariate Cox proportional hazards regression models

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Metformin use	0.68 (0.52–0.89)	0.004	0.64 (0.48–0.86)	0.003
Tumor size, cm	1.15 (1.07–1.24)	<0.001	1.04 (0.96–1.14)	0.359
Tumor site (tail)	1.42 (1.21–2.00)	0.045	0.75 (0.48–1.17)	0.200
Stage				
Resectable	1.00		1.00	
Unresectable	3.10 (2.11–4.55)	<0.001	3.05 (2.01–4.63)	<0.001
Metastatic	5.38 (3.64–7.94)	<0.001	5.27 (3.31–8.40)	<0.001
CA-19-9, U/mL				
0—47	1.00		1.00	
>47–1,000	1.75 (1.16–2.64)	0.008	1.57 (1.02–2.44)	0.039
>1,000	3.29 (2.13–5.06)	<0.001	2.22 (1.39–3.55)	0.001
Performance status				
0	1.00		1.00	
1	1.34 (0.92–1.96)	0.130	0.92 (0.60–1.39)	0.682
2	1.99 (1.23–3.21)	0.005	0.94 (0.55–1.61)	0.814
3	2.73 (1.30–5.75)	0.008	2.49 (1.11–5.60)	0.028

76% of the patients, it was challenging for the patients to accurately recall their medication history. Furthermore, the study did not take into consideration the impact of the dose at which metformin was administered, the joint effect of other antidiabetic agents, or the glycemic control status. In our study, more patients in the non-metformin group than in the metformin group were treated with insulin. Even though the impact of glycemic control on pancreatic cancer outcome is unknown, there is a concern that patients who used insulin may have had a poor glucose control by using oral medications or had a poor performance status which precluded the use of oral medications. However, our data showed that insulin use was not related to the risk of death. Metformin use reduced the risk of death in both insulin and non-insulin groups. In addition, other oral antidiabetic medications did not show any significant association with the risk of death; therefore, the survival differences in metformin and non-metformin group could not be explained by the patient performance status or insulin use. We also observed that more patients in the metformin group than in the non-metformin group had tumors of the pancreatic tail. Because tumors of the pancreatic tail are often diagnosed at the metastatic stage, the survival benefit of metformin use was either underestimated or not affected by this imbalance. In fact, we did not observe a significant association of metformin use and overall survival in patients with metastatic disease. The lack of efficacy in this group may be explained by a small sample size, a modest antitumor effect of metformin, large tumor burden, and potential difference in tumor biology in metastatic disease. Because information on the duration of metformin use was not collected in our early study and was not available from patients' medical records, we were able to examine the association between the duration of metformin use and survival in 89 patients only. A weak beneficial effect of metformin use for 2 to 5 years on survival over a short-term use of less than 2 years was observed, and long-term metformin use for more than 5 years did not show further improvement on survival. These observations need to be confirmed in a larger study with detailed information on the dose of metformin use to clarify the dose–response relationship.

Our study suggests that metformin may improve the OS rates of patients with diabetes and nonmetastatic pancreatic cancer independent of other known prognostic factors. The

Table 4. Duration of metformin use and OS

Metformin use, y	No. of patients (no. of deaths)	Mean ± SE of survival time	HR[a] (95% CI)	*P*
<2	47 (34)	19.2 ± 1.9	1.0	
2–5	22 (13)	28.7 ± 4.9	0.54 (0.28–1.05)	0.069
>5	20 (13)	26.9 ± 5.5	0.82 (0.40–1.69)	0.594
>2 (2–5 and >5)	42 (26)	27.6 ± 3.7	0.64 (0.37–1.10)	0.109

[a]HR (95% CI) was adjusted for stage and serum level of CA-19-9.

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

antitumor effect of metformin may translate into clinical benefit in the form of improved response to chemotherapy and prolonged survival. Findings from this retrospective study need to be confirmed in other patient populations. Future prospective studies are also required to validate the results of our study, assess the dose/duration effect, and address the safety and efficacy of this treatment in nondiabetic patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by the NIH through RO1 grant CA98380 (D. Li), SPORE P20 grant CA101936 (J.L. Abbruzzese), and MD Anderson's Cancer Center Support Grant CA016672, as well as a Multidisciplinary Research Program grant from MD Anderson Cancer Center (S.-C. J. Yeung).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 22, 2011; revised February 16, 2012; accepted February 18, 2012; published OnlineFirst March 31, 2012.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49.
2. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009;6:699–708.
3. American Cancer Society. Cancer facts and figures 2011. Atlanta, GA: American Cancer Society; 2011.
4. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605–9.
5. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076–83.
6. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JMM. New users of metformin are at low risk of incident cancer. Diabetes Care 2009;32:1620–5.
7. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–77.
8. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ, et al. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care 2010;33:322–6.
9. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR, Bodmer M, et al. Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 2010;33:1304–8.
10. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD, Evans JMM, et al. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304–5.
11. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254–8.
12. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137:482–8.
13. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 2010;116:1938–46.
14. Donadon V, Balbi M, Ghersetti M, Grazioli S, Perciaccante A, Della Valentina G, et al. Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. World J Gastroenterol 2009;15:2506–11.
15. Wright JL, Stanford JL, Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. Cancer Causes Control 2009;20:1617–22.
16. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009;27:3297–302.
17. Magruder JT, Elahi D, Andersen DK. Diabetes and pancreatic cancer: chicken or egg? Pancreas 2011;40:339–51.
18. Alimova IN, Liu B, Fan Z, Edgerton SM, Dillon T, Lind SE, et al. Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest *in vitro*. Cell Cycle 2009;8:909–15.
19. Cazzaniga M, Bonanni B, Guerrieri-Gonzaga A, Decensi A. Is it time to test metformin in breast cancer clinical trials? Cancer Epidemiol Biomarkers Prev 2009;18:701–5.
20. Goodwin PJ, Ligibel JA, Stambolic V. Metformin in breast cancer: time for action. J Clin Oncol 2009;27:3271–3.
21. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007;102:2696–707.
22. Wang F, Herrington M, Larsson J, Permert J. The relationship between diabetes and pancreatic cancer. Mol Cancer 2003;2:4.
23. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Erratum appears in Nat Rev Cancer. 2009 Mar;9(3):224. Nat Rev Cancer 2008;8:915–28.
24. Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, et al. Effect of metformin on life span and on the development of spontaneous mammary tumors in HER-2/neu transgenic mice. Exp Gerontol 2005;40:685–93.
25. Hou M, Venier N, Sugar L, Musquera M, Pollak M, Kiss A, et al. Protective effect of metformin in CD1 mice placed on a high carbohydrate-high fat diet. Biochem Biophys Res Commun 2010;397:537–42.
26. Phoenix KN, Vumbaca F, Fox MM, Evans R, Claffey KP, Phoenix KN, et al. Dietary energy availability affects primary and metastatic breast cancer and metformin efficacy. Breast Cancer Res Treat 2010;123:333–44.
27. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, Dennis PA. Metformin prevents tobacco carcinogen-induced lung tumorigenesis. Cancer Prev Res 2010;3:1066–76.
28. Ben Sahra I, Laurent K, Loubat A, Giorgetti-Peraldi S, Colosetti P, Auberger P, et al. The antidiabetic drug metformin exerts an antitumoral effect *in vitro* and *in vivo* through a decrease of cyclin D1 level. Oncogene 2008;27:3576–86.
29. Buzzai M, Jones RG, Amaravadi RK, Lum JJ, DeBerardinis RJ, Zhao F, et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. Cancer Res 2007;67:6745–52.
30. Feng YH, Velazquez-Torres G, Gully C, Chen J, Lee MH, Yeung SC. The impact of type 2 diabetes and antidiabetic drugs on cancer cell growth. J Cell Mol Med 2011;15:825–36.
31. Kisfalvi K, Eibl G, Sinnett-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. Cancer Res 2009;69:6539–45.
32. Zakikhani M, Dowling R, Fantus IG, Sonenberg N, Pollak M. Metformin is an AMP kinase-dependent growth inhibitor for breast cancer cells. Cancer Res 2006;66:10269–73.
33. Rozengurt E, Sinnett-Smith J, Kisfalvi K, Rozengurt E, Sinnett-Smith J, Kisfalvi K. Crosstalk between insulin/insulin-like growth factor-1 receptors and G protein-coupled receptor signaling systems: a novel target for the antidiabetic drug metformin in pancreatic cancer. Clin Cancer Res 2010;16:2505–11.
34. Schneider MB, Matsuzaki H, Haorah J, Ulrich A, Standop J, Ding XZ, et al. Prevention of pancreatic cancer induction in hamsters by metformin. Gastroenterology 2001;120:1263–70.

Published OnlineFirst March 31, 2012; DOI: 10.1158/1078-0432.CCR-11-2994

35. Bao B, Wang Z, Li Y, Kong D, Ali S, Banerjee S, et al. The complexities of obesity and diabetes with the development and progression of pancreatic cancer. Biochim Biophys Acta 2011;1815:135–46.
36. Williams T, Brenman JE. LKB1 and AMPK in cell polarity and division. Trends Cell Biol 2008;18:193–8.
37. Ben Sahra I, Regazzetti C, Robert G, Laurent K, Le Marchand-Brustel Y, Auberger P, et al. Metformin, independent of AMPK, induces mTOR inhibition and cell-cycle arrest through REDD1. Cancer Research 2011;71:4366–72.
38. Kalender A, Selvaraj A, Kim SY, Gulati P, Brule S, Viollet B, et al. Metformin, independent of AMPK, inhibits mTORC1 in a rag GTPase-dependent manner. Cell Metab 2010;11:390–401.
39. Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer Res 2009;69:7507–11.
40. Pollak M. Metformin and other biguanides in oncology: advancing the research agenda. Cancer Prev Res (Phila) 2010;3:1060–65.
41. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F, Ben Sahra I, Le Marchand-Brustel Y, et al. Metformin in cancer therapy: a new perspective for an old antidiabetic drug?Mol Cancer Ther 2010;9:1092–9.
42. Li D. Metformin as an antitumor agent in cancer prevention and treatment. J Diabetes 2011;3:320–7.
43. Yang YX. Do diabetes drugs modify the risk of pancreatic cancer? Gastroenterology 2009;137:412–5.

AACR American Association for Cancer Research

Clinical Cancer Research

Metformin Use Is Associated with Better Survival of Diabetic Patients with Pancreatic Cancer

Navid Sadeghi, James L. Abbruzzese, Sai-Ching J. Yeung, et al.

Clin Cancer Res 2012;18:2905-2912. Published OnlineFirst March 31, 2012.