ORIGINAL ARTICLE

Survival of Patients with Stage IV Lung Cancer with Diabetes Treated with Metformin

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Abstract

Rationale: Prior studies have shown an anticancer effect of metformin in patients with breast and colorectal cancer. It is unclear, however, whether metformin has a mortality benefit in lung cancer.

Objectives: To compare overall survival of patients with diabetes with stage IV non–small cell lung cancer (NSCLC) taking metformin versus those not on metformin.

Methods: Using data from the Surveillance, Epidemiology, and End Results registry linked to Medicare claims, we identified 750 patients with diabetes 65–80 years of age diagnosed with stage IV NSCLC between 2007 and 2009. We used propensity score methods to assess the association of metformin use with overall survival while controlling for potential confounders.

Measurements and Main Results: Overall, 61% of patients were on metformin at the time of lung cancer diagnosis. Median survival in the metformin group was 5 months, compared with 3 months in patients not treated with metformin ($P < 0.001$). Propensity score analyses showed that metformin use was associated with a statistically significant improvement in survival (hazard ratio, 0.80; 95% confidence interval, 0.71–0.89), after controlling for sociodemographics, diabetes severity, other diabetes medications, cancer characteristics, and treatment.

Conclusions: Metformin is associated with improved survival among patients with diabetes with stage IV NSCLC, suggesting a potential anticancer effect. Further research should evaluate plausible biologic mechanisms and test the effect of metformin in prospective clinical trials.

Keywords: lung neoplasms; diabetes; metformin; survival analysis

At a Glance Commentary

Scientific Knowledge on the Subject: Metformin has been found to have anticancer activity in preclinical models and seems to be associated with improved survival among patients with diabetes with breast, prostate, and colorectal cancer. Little is known about the potential effect of metformin on survival in patients with lung cancer.

What This Study Adds to the Field: Using a population-based cancer registry, we determine that metformin use is associated with improved survival among patients with diabetes with stage IV non–small cell lung cancer, after controlling for potential confounders. These findings suggest that metformin may have an anti–lung cancer effect.

There is increasing interest in investigating the repurposing of already-approved medications as possible cancer chemotherapeutic agents (1–3). The use of these medications offers several advantages to traditional drug development, including an established safety profile and shorter timeline for regulatory evaluation. Among the medications being evaluated,

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metformin, a biguanide derivative commonly used to treat type II diabetes, has been found to have anticancer activity in preclinical models (4, 5).

Patients with diabetes are at higher risk for developing cancer, including breast, colorectal, pancreatic, and lung malignancies (6–9). Furthermore, diabetes seems to worsen cancer-specific and overall survival in several cancers (10–13). Among patients with diabetes, metformin has been associated with a decreased overall risk for developing certain cancers (14, 15). Metformin also seems to be associated with improved survival among patients with diabetes with breast, prostate, and colorectal cancer (14, 16, 17).

There are little data regarding the effects of metformin use on lung cancer prognosis. One small retrospective study from China showed that patients with diabetes with lung cancer treated with metformin had improved overall and progression-free survival (18). However, the effect of metformin on lung cancer outcomes has not been validated in larger samples.

In this study, we used a nationally representative, population-based cancer data source in the United States to determine the effect of metformin use on survival outcomes among patients with diabetes with stage IV non–small cell lung cancer (NSCLC).

Methods

The study was conducting using the Surveillance, Epidemiology, and End Results (SEER) registry (2007–2009) linked to Medicare claims (19). We selected patients with diabetes greater than or equal to 65 years with histologically confirmed stage IV NSCLC. We excluded individuals in health care maintenance organizations or those without Part B Medicare insurance because of a lack of complete claims and those without Part D coverage for whom we could not ascertain outpatient medications (20). To avoid patients who would not have been metformin candidates, we excluded patients older than 80 years, or those with stage IV–V chronic kidney disease or end-stage renal disease, or those not taking any diabetic medication. We excluded patients living in a nursing home at time of diagnosis because they likely had limited functional status.

Sociodemographics and Comorbidities

Sociodemographic information was obtained from the SEER and Medicare databases. We used the Deyo adaptation of Charlson index to assess the burden of comorbidities (21–23) and data about use of home health services (restricted to homebound patients) as a proxy for poor performance status (24).

Diabetes and Diabetic Regimen

We identified patients with diabetes using a validated algorithm based on presence of *International Classification of Diseases, Ninth Revision* codes (250.xx) prior to lung cancer diagnosis. Diabetes-related complications and end-organ damage were summarized using a validated, claims-based severity score (25). Diabetes medication use was ascertained from Medicare Part D claims. Patients were classified as using specific drugs if there was a pharmacy claim submitted within 6 months prior to cancer diagnosis. Medications were classified as follows: metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, and insulin.

Cancer-related Factors and Treatment

Tumor location and histology were obtained from SEER; histologic subtypes were classified using *International Classification of Diseases for Oncology* (26). We ascertained use of diagnosis and staging procedures from Medicare claims. Using validated claim-based algorithms, we classified patients as treated with chemotherapy if they received treatment within 4 months of NSCLC diagnosis (27). Receipt of radiation therapy was ascertained using SEER and Medicare data (28).

Study Outcome

The study outcome was overall survival determined from Medicare data. Survival times were calculated as the period from the date of diagnosis to the date of death; subjects alive as of December 15, 2011 were censored.

Table 1. Baseline Characteristics of Patients with Stage IV Non–Small Cell Lung Cancer with Diabetes in the SEER-Medicare Database, 2007–2009

Characteristic	Metformin (*n* = 458)	No Metformin (*n* = 292)	*P* Value	Adjusted *P* Value*
Age, yr, mean ± SD	72.2 ± 4.0	72.7 ± 4.0	0.09	0.98
Male, n (%)	233 (52.8)	164 (57.8)	0.19	0.99
Married, n (%)	212 (48.1)	135 (47.5)	0.89	0.99
Race/ethnicity, n (%)			0.25	0.99
White	297 (67.4)	187 (65.9)		
Black	57 (12.9)	50 (17.6)		
Hispanic	45 (10.2)	21 (7.4)		
Other	42 (9.5)	26 (9.2)		
Income, n (%)			0.23	0.99
First quartile	153 (34.8)	101 (35.6)		
Second quartile	91 (20.7)	70 (24.7)		
Third quartile	99 (22.5)	67 (23.6)		
Fourth quartile	97 (25.1)	46 (16.2)		
Diabetes severity index score, median (IQR)	4 (3)	5 (4)	0.17	0.99
Comorbidity score, n (%)			0.02	0.96
<1	194 (42.4)	115 (39.4)		
1–2	121 (26.4)	59 (20.2)		
>2	143 (31.2)	118 (40.4)		
Diabetes medications, n (%)				
Sulfonylureas	234 (51.1)	172 (58.9)	0.04	0.98
Meglitinides	25 (5.5)	24 (8.2)	0.14	0.91
Thiazolidinediones	159 (34.7)	108 (37.0)	0.53	0.99
DPP-4 inhibitors	34 (7.4)	19 (6.5)	0.63	0.97
α-Glucosidase inhibitors	≤11 (≤2.5)	≤11 (≤4.0)	0.93	0.99
Insulin	121 (26.4)	112 (38.4)	<0.01	0.77

Definition of abbreviations: DPP-4 = dipeptidyl peptidase-4; IQR = interquartile range.
**P* values for analysis adjusting for propensity scores.

Statistical Analysis

Baseline characteristics were compared between patients using metformin versus other diabetes medications using the *t* test, chi-square test, or Wilcoxon test. Unadjusted Kaplan-Meier curves were plotted for patients treated with or without metformin and compared using the log-rank test.

We used propensity score methods to control for potential allocation bias (29) because differences in patient characteristics and diabetes severity may have influenced use of metformin. The propensity score represents the probability that a patient will receive a treatment based on their known characteristics. We calculated propensity scores using a logistic model that included patients' sociodemographics, comorbidities, performance status, diabetes medications, and diabetes severity score and used regression analysis to evaluate whether covariates were balanced across treatment groups.

Cox regression was used to compare survival of patients on metformin versus other medications adjusting for propensity scores and use of positron emission tomography scan, tumor characteristics, and use of chemotherapy. Adjusted analyses were performed using inverse probability weighting, fitting a stratified Cox model according to propensity score quintiles, and matching patients by propensity scores (30). We conducted secondary stratified analyses by receipt of chemotherapy, insulin treatment, and other oral medication use. Additionally, to assess if the survival benefit was specific to metformin, we tested the effect of insulin or other oral medications among patients not receiving metformin. Analyses were performed with SAS 9.3 (SAS, Cary, NC) using two-tailed *P* values. Our study was deemed exempt following institutional review board evaluation.

Results

We identified 1,177 patients aged 65–80 years with diabetes at the time of diagnosis with stage IV NSCLC. We excluded 394 patients who were not on diabetes medications and 33 individuals who were in a nursing home at time of diagnosis; the final cohort consisted of 750 patients. Overall, 492 (61%) patients were treated with metformin at time of lung cancer diagnosis; median time of metformin use was 26.7 months among the cohort diagnosed in 2009 (who had Medicare Part D coverage since 2007). Metformin-treated patients were more likely to have fewer comorbidities ($P = 0.02$) and, as expected, were less likely to receive sulfonylureas ($P = 0.04$) or insulin ($P < 0.01$) (Table 1). All other baseline characteristics were not significantly different between the two groups and all covariates were well-balanced after adjustment for propensity scores (Table 1). Those in the metformin group were more likely to have had a positron emission tomography scan ($P = 0.02$) (Table 2); all other cancer-staging variables (mediastinoscopy, fine-needle biopsy, and bone scan) were similar between the two groups. Metformin-treated patients were also more likely to have been treated with chemotherapy ($P = 0.02$), but there was no difference between the groups for erlotinib therapy.

Unadjusted median overall survival for those in the metformin group was

Table 2. Lung Cancer and Treatment Characteristics of Study Subjects

Characteristic	Metformin (*n* = 458)	No Metformin (*n* = 292)	*P* Value
Tumor histology, n (%)			0.69
Adenocarcinoma	276 (62.6)	172 (60.6)	
Squamous cell	120 (27.2)	82 (28.9)	
Large cell or other	45 (10.2)	30 (10.5)	
Tumor site, n (%)			0.80
Upper lobe	202 (45.8)	133 (46.8)	
Middle/lower lobe	139 (31.5)	81 (28.5)	
Other	100 (22.7)	70 (24.7)	
Mediastinoscopy, n (%)	12 (2.8)	≤11 (≤4.0)	0.25
PET scan, n (%)	163 (37.9)	81 (29.5)	0.02
Bone scan, n (%)	83 (19.3)	43 (15.6)	0.22
Fine-needle aspiration, n (%)	113 (25.6)	73 (25.7)	0.98
Chemotherapy, n (%)	227 (51.5)	122 (43.0)	0.03
Erlotinib, n (%)	66 (14.4)	36 (12.3)	0.42

Definition of abbreviation: PET = positron emission tomography.

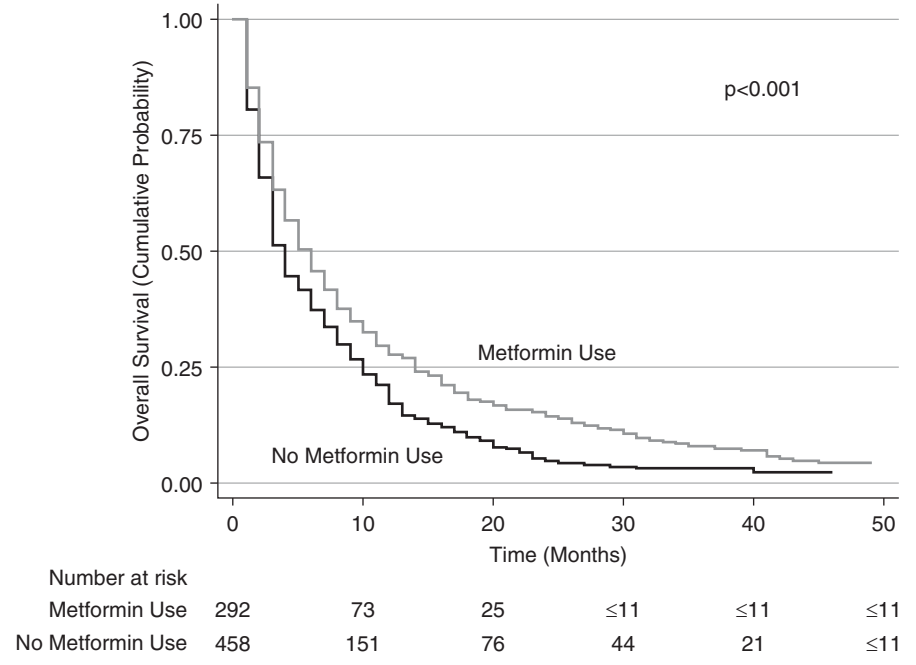

Figure 1. Kaplan-Meier survival curves for all patients in cohort. Patients in the metformin group have better overall survival than those in the nonmetformin group.

Table 3. Propensity Score Analysis: Comparison of Survival of Patients Treated with and without Metformin

Model	Hazard Ratio (95% CI)
Primary analysis: entire cohort	
Inverse probability weighted	0.80 (0.71–0.89)
Stratified by propensity score quintiles	0.79 (0.61–0.93)
Matched analysis (n = 708)	0.73 (0.62–0.87)
Secondary analyses	
Chemotherapy-treated patients	
Inverse probability weighted	0.77 (0.65–0.92)
Stratified by propensity score quintiles	0.77 (0.60–0.98)
Matched analysis (n = 340)	0.75 (0.58–0.97)
Nonchemotherapy-treated patients	
Inverse probability weighted	0.83 (0.71–0.97)
Stratified by propensity score quintiles	0.86 (0.69–1.08)
Matched analysis (n = 368)	0.77 (0.61–0.99)
Insulin-treated patients	
Inverse probability weighted	0.76 (0.61–0.95)
Stratified by propensity score quintiles	0.70 (0.52–0.93)
Matched analysis (n = 218)	0.65 (0.48–0.88)
Noninsulin-treated patients	
Inverse probability weighted	0.79 (0.69–0.92)
Stratified by propensity score quintiles	0.83 (0.67–1.02)
Matched analysis (n = 490)	0.77 (0.62–0.95)
Other oral medication–treated patients	
Inverse probability weighted	0.74 (0.65–0.84)
Stratified by propensity score quintiles	0.71 (0.59–0.85)
Matched analysis (n = 520)	0.65 (0.53–0.80)

Definition of abbreviation: CI = confidence interval.
The hazard ratio represents the risk of death of a patient treated with metformin compared with a patient who did not receive metformin. All models were also adjusted for tumor histology, tumor site, receipt of positron emission tomography scan, and use of chemotherapy.

5 months (interquartile range, 12 mo) compared with 3 months among those not treated with metformin (interquartile range, 8 mo; $P < 0.001$) (Figure 1). Inverse probability weighting analyses using Cox regression (and adjusted for staging work-up, cancer characteristics, and chemotherapy use) showed that metformin was associated with significantly better overall survival (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.71–0.89) (Table 3). The survival advantage with metformin persisted when the analyses were repeated using stratification (HR, 0.79; 95% CI, 0.61–0.93) or matching (HR, 0.73; 95% CI, 0.62–0.87) of study patients by propensity scores.

Unadjusted (Figure 2) and adjusted (Table 3) secondary analysis stratified by receipt of chemotherapy (HR, 0.77; 95% CI, 0.65–0.92), insulin treatment (HR, 0.76; 95% CI, 0.61–0.95), or other oral diabetes medications (HR, 0.73; 95% CI, 0.65–0.83) also showed a significant survival advantage conferred by metformin use. The survival benefit of metformin remained significant when secondary analyses were repeated using stratification or matching of patients by propensity scores. However, analyses excluding those on metformin showed that use of other oral diabetes medications did not confer a survival benefit (HR, 0.88; 95% CI, 0.65–1.20) in the insulin-treated group. Similarly, insulin was not associated with improved survival (HR, 0.97; 95% CI, 0.79–1.20) in patients on other (nonmetformin) oral medications.

Discussion

Prior studies have reported a survival benefit with metformin use in breast, prostate, and colorectal cancer; however, there are limited data regarding the potential effectiveness of this drug among patients with lung cancer. Using population-based data, we found that among patients with stage IV NSCLC with preexisting diabetes, metformin compared with other diabetic medications was associated with significantly better survival. Our results contribute further evidence supporting the potential anticancer effects of metformin. Randomized clinical trials of metformin as an adjunctive treatment of lung cancer, and deeper investigation into its underlying biologic mechanisms, are likely warranted.

There have been few publications examining metformin's influence on lung cancer risk (31–34). These studies show varying results regarding metformin and risk for developing lung cancer and lung cancer prognosis. In a retrospective case-control study, Mazzone and colleagues (31) found that metformin was associated with a more aggressive lung cancer phenotype and worse prognosis. Conversely, two observational studies, a small Chinese study with patients with lung cancer and a larger UK study that included many cancer types, showed that metformin was associated with improved survival in patients with lung cancer (17, 18). A major limitation of these studies is the lack of adjustment for baseline patient characteristics that might account for metformin use. Moreover, in these studies, all stages of lung cancer were included and the analyses did not control for differences in lung cancer treatment. Our study is the first to show the association of metformin with improved survival in a large, unselected sample of patients with stage IV NSCLC, after controlling and stratifying by use of other diabetic medications and chemotherapy. Consistent with the prior studies, we found that metformin was associated with an almost 20% improvement in overall survival among subjects with diabetes with metastatic lung cancer.

Although the mechanisms are not yet fully understood, there are two potential pathways through which metformin may have an anticancer effect. NSCLC expresses the insulin receptor, and high levels of insulin receptor expression have been associated with faster cancer progression and decreased survival (35). Metformin reduces insulin resistance and circulating insulin levels, thereby attenuating the stimulatory effect of insulin (36). Mouse models of lung cancer, using doses of metformin that are physiologically relevant to humans, have found that metformin administration led to decreased circulating concentrations of insulin and insulin-like growth factor-1 and in lung tissue, reduced activation of insulin receptor/insulin-like growth factor-1 receptor, decreased

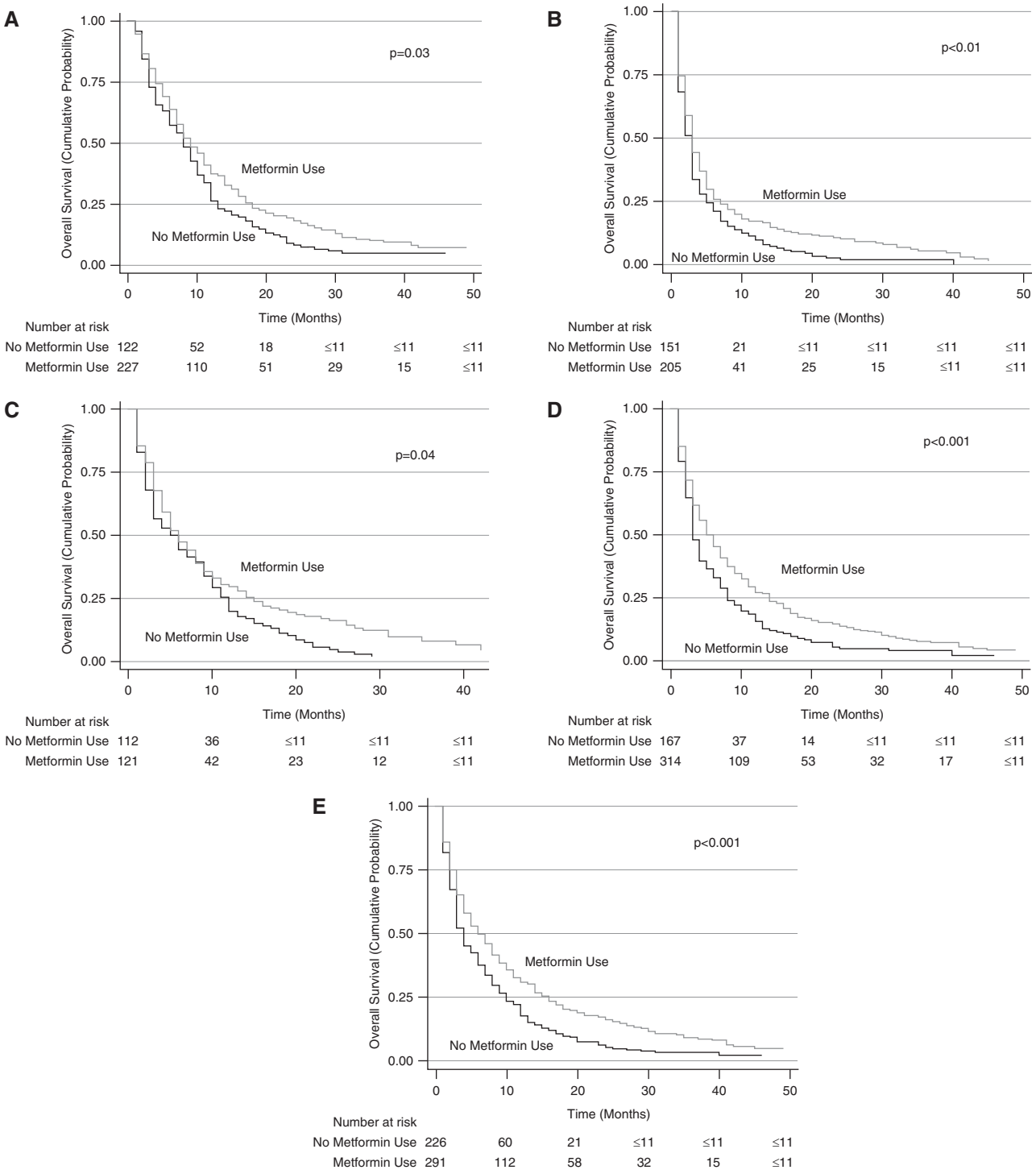

Figure 2. Stratified Kaplan-Meier survival curves. Stratified by patients who received chemotherapy (*A*), patients who did not receive chemotherapy (*B*), patients who were treated with insulin (*C*), patients who were not treated with insulin (*D*), and patients who were treated with other oral medications (*E*).

downstream signaling, and diminished cancer cell proliferation (37). Supporting this theory, we found that among patients treated with insulin, metformin use conferred a significant survival benefit and may therefore attenuate the cancer-promoting effects of insulin. Conversely, other oral medications were not associated with an improved survival, suggesting that the effect is specific to metformin.

Metformin may also act directly on tumor cells by altering intracellular signaling pathways leading to a decrease in cell proliferation (38–43). *In vitro* and animal-based studies have reported

that metformin inhibits NSCLC growth by activation of adenosine monophosphate–activated protein kinase in tumor cells (38). Activation of adenosine monophosphate–activated protein kinase down-regulates protein, cholesterol, and glycogen synthesis pathways and inhibits cell proliferation (44, 45). Combination therapy with metformin and doxorubicin also has been shown to inhibit lung tumor growth in animal studies, even when doxorubicin doses were reduced to subtherapeutic levels (46). Similarly, we found that even after controlling for receipt of chemotherapy, those in the metformin group had better overall survival, thus suggesting a potential independent cancer therapeutic effect of metformin.

Several strengths and limitations of this study should be noted. First, because of the observational nature of the study, treatment with metformin was not randomized. To address this limitation, we excluded patients who would not have been eligible for metformin therapy and adjusted our analyses for potential confounders, such as comorbidities, other diabetes medications, and diabetes severity to create a comparison group that would have had similar likelihoods of receiving metformin. Patients with NSCLC who were treated with metformin were more likely to receive chemotherapy and less likely to be on insulin; however, the survival benefit of metformin was consistent even after stratifying by these factors. We were also unable to assess glycemic control and therefore could not evaluate the potential benefit of metformin through its effect of diabetes outcomes. For this reason, we studied a cohort of patients with stage IV NSCLC, because most of these patients die of cancer progression rather than competing risks of death; thus, the potential effect of diabetes control should be marginal. We were also unable to assess the effect of metformin in younger patients and we did not assess the effect in patients without diabetes. Moreover, our cohort included many older patients with considerable number of comorbidities, many of whom did not receive chemotherapy. Thus, these findings may not be generalizable to healthier individuals with lung cancer.

Use of diabetes medications was determined using pharmacy claims, and therefore we have no information on adherence to therapy. Despite this, pharmacy claims data have been shown to have high concordance with pill counts (47). We used a conservative estimate of medication treatment because some patients receive a 3-month supply of their chronic medications. Furthermore, lack of adherence would have biased our results toward the null. Finally, we were not able to assess whether there was a dose-dependent effect of metformin on overall survival. Consistent with an intention-to-treat analysis, we did not include metformin use after lung cancer diagnosis because ongoing use of metformin after cancer diagnosis may suggest a healthier population.

In summary, these data suggest that among patients with diabetes and stage IV NSCLC, metformin use was associated with improved survival. This effect is consistent with the survival benefit of metformin observed in other cancer types. Further prospective studies evaluating the use of metformin in conjunction with chemotherapy for stage IV lung cancer can help determine if metformin is an effective treatment for lung cancer. ■

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