Research Article

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Metformin Use and Lung Cancer Risk in Patients with Diabetes

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Abstract

Methodologic biases may explain why observational studies examining metformin use in relation to lung cancer risk have produced inconsistent results. We conducted a cohort study to further investigate this relationship, accounting for potential biases. For 47,351 patients with diabetes ages ≥40 years, who completed a health-related survey administered between 1994 and 1996, data on prescribed diabetes medications were obtained from electronic pharmacy records. Follow-up for incident lung cancer occurred from January 1, 1997, until June 30, 2012. Using Cox regression, we estimated lung cancer risk associated with new use of metformin, along with total duration, recency, and cumulative dose (all modeled as time-dependent covariates), adjusting for potential confounding factors. During 428,557 person-years of follow-up, 747 patients were diagnosed with lung cancer. No association was found with duration, dose, or recency of metformin use and overall lung cancer risk. Among never smokers, however, ever use was inversely associated with lung cancer risk [HR, 0.57; 95% confidence interval (CI), 0.33–0.99], and risk appeared to decrease monotonically with longer use (≥5 years: HR, 0.48; 95% CI, 0.21–1.09). Among current smokers, corresponding risk estimates were >1.0, although not statistically significant. Consistent with this variation in effect by smoking history, longer use was suggestively associated with lower adenocarcinoma risk (HR, 0.69; 95% CI, 0.40–1.17), but higher small cell carcinoma risk (HR, 1.82; 95% CI, 0.85–3.91). In this population, we found no evidence that metformin use affects overall lung cancer risk. The observed variation in association by smoking history and histology requires further confirmation. *Cancer Prev Res; 8(2); 174–9. ©2014 AACR.*

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Introduction

Metformin is commonly prescribed as first-line treatment for type II diabetes. Systemically, this biguanide drug improves blood glucose control and insulin sensitivity by lowering hepatic glucose production and intestinal glucose absorption and stimulating peripheral glucose uptake. Metformin may further possess chemopreventive and chemotherapeutic properties against cancer, although the underlying molecular mechanisms are not well understood (1, 2).

At the cellular level, metformin alters mitochondrial respiratory chain activity, inducing energy stress and reduced ATP production (3). Among the affected cellular pathways likely relevant to carcinogenesis is the activation of AMP-activated protein kinase (AMPK) by liver kinase B1 (LKB1, a protein encoded by a known tumor-suppressor gene), which leads to decreased growth factor signaling, protein and lipid synthesis, and proliferation via mTOR inhibition. Growing evidence suggests that metformin also elicits cytostatic effects through AMPK-independent mechanisms (3, 4).

Metformin appears to suppress lung tumor growth in obese, hyperinsulinemic mice by increasing insulin sensitivity and activating AMPK (5). Metformin has been additionally shown to reduce lung tumor burden, but not tumor incidence, in nondiabetic mice exposed to the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; ref. 6). In this latter study, the corresponding inhibition of mTOR was associated with decreased phosphorylation of the insulin-like growth factor-I receptor/insulin receptor and not with AMPK activation. More recently, the metformin analogue phenformin was found to decrease tumor burden and increase survival in mice with Lkb1-deficient lung tumors (7).

Results from the observational studies examining whether metformin use is associated with lung cancer risk in patients with diabetes have been less consistent (8–15). Metformin use has been reported to reduce risk (10, 12–14) or have no relation (8, 9, 11, 15). Several time-related biases may explain in part why inverse associations have been detected (16, 17). Such biases can be introduced when unexposed time is misclassified as exposed in time-fixed analyses (immortal time bias), when the time window for capturing exposure differs between cases and controls (time-window bias), or when treatment differs across stages of the disease being treated and disease stage is also associated with risk of the outcome (time-lag bias). In the most rigorous study of metformin use and lung cancer risk to date, no association was found when evaluating dose–response by cumulative duration or dose and subgroup differences by smoking status (11).

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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In prior work assessing cancer risk in relation to pioglitazone use among Kaiser Permanente Northern California (KPNC) health plan members with diabetes, we noted that lung cancer incidence was not associated with ever use of metformin (15). Herein, we more comprehensively examine this drug–cancer relationship in a well-defined subset of that patient cohort (i.e., adults ages ≥40 years with diabetes who completed a baseline health-related survey), now with up to 15 years of follow-up. To mitigate methodologic biases, we evaluated lung cancer risk associated with new use of metformin, accounting for time-varying exposure to metformin and other diabetes medications and adjusting for diabetes duration, smoking history, and other potential confounding factors. We also evaluated the association of metformin use, in terms of total duration, recency of use, and cumulative dose, and lung cancer risk, and the consistency of such associations by gender, smoking history, and tumor histology and stage.

Materials and Methods

Study design and population

This retrospective cohort study was conducted under a waiver of informed consent approved by the KPNC Institutional Review Board. KPNC is a large integrated health care delivery system, with an enrolled membership that is generally representative of the insured population in Northern California, except for extremes of the socioeconomic spectrum (18).

Study eligibility was limited to persons in the KPNC Diabetes Registry (19, 20), who completed a health survey administered from 1994 to 1996 and were ≥40 years of age at baseline (January 1, 1997). The KPNC Diabetes Registry was established in 1993 to capture all health plan members with diabetes from automated databases on an annual basis, who meet at least one of the following criteria: a primary hospital discharge diagnosis of diabetes; at least two outpatient visit diagnoses of diabetes; any prescription of a diabetes-related medication; and any laboratory record of an abnormal hemoglobin A1c (HbA1c) test. At baseline, those who lacked continuous KPNC membership for at least 2 years, had previously used metformin, or had a prior cancer were excluded. These exclusion criteria ensured a more complete assessment of patients' medical history, including prescribed medications and comorbid conditions; examination of new metformin users only; and identification of incident cancer diagnoses during follow-up, respectively.

Exposure and outcome measures

Record linkage to the KPNC pharmacy database permitted identification of all prescribed diabetes medications filled from January 1, 1995, onward for each patient. Diabetes medications included metformin, sulfonylureas, thiazolidinediones, insulin, and other oral agents. Metformin was first available as part of the KPNC formulary in May 1995 (21).

Patients were defined as ever users of a given diabetes medication if they had filled two or more prescriptions for that medication within a 6-month period. Total duration of metformin use was calculated as the number of days supplied for each metformin prescription. Recency of metformin use was defined into mutually exclusive categories of former use, recent use, or current use for <5 or ≥5 years. Current use encompassed the period(s) of days supplied. Recent use encompassed the 1-year period after end of current use, whereas former use encompassed the period more than 1 year after end of current use. Cumulative dose was calculated as the total prescribed dose, defined as the number of pills supplied per prescription multiplied by the dose per pill, for all prescriptions of metformin dispensed until the end of follow-up. If a prescription was not used entirely when follow-up ended, then total duration and prescribed cumulative dose were adjusted, only counting pills taken before the end of follow-up.

Data on the following potential confounders were collected by survey: race/ethnicity, smoking status, and pack-year history, alcohol use, income, education level, diabetes duration, and body mass index (BMI). Baseline HbA1c and creatinine levels were obtained from laboratory records. Charlson comorbidity index scores were derived using data on comorbid conditions documented in outpatient and inpatient visit records in the 2 years before baseline (22).

Patients diagnosed with lung and other cancers were identified by record linkage to the KPNC Cancer Registry. All data elements in the KPNC Cancer Registry, including tumor stage and histology, are ascertained following standards of the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results Program.

Statistical analysis

Patients were followed from baseline until diagnosis of lung or another cancer, a gap of ≥4 months in membership or prescription benefits, death, or study close (June 30, 2012), whichever occurred earliest. To avoid immortal time bias (i.e., misclassification of unexposed time as exposed), person-time from the start of follow-up until first use of a given medication was classified as never use for that medication. Once the definition of ever use was met, a patient was classified as a user of that medication, even if discontinuation occurred later.

Point estimates and 95% confidence intervals of the relative hazards for lung cancer associated with ever use of metformin, along with total duration, recency of use, and cumulative dose, were calculated using Cox regression. The reference group was never users of metformin, which included users of other diabetes medications. Measures of metformin (i.e., ever use, total duration, recency of use, cumulative dose) and other classes of diabetes medications (i.e., sulfonylureas, thiazolidinediones, insulin, all others), in addition to two separate covariates, indicating never use of any diabetes medication and never having two prescriptions of the same medication filled within 6 months, were modeled as time-dependent covariates. Regression models were stratified on age and adjusted for other potential confounding variables selected *a priori*, including gender, race/ethnicity, median household income, education level, ever use of other diabetes medications, diabetes duration, smoking status, pack-years smoked, alcohol use, baseline creatinine and HbA1c levels, BMI, and Charlson comorbidity index.

Following the same approach, analyses lagging metformin use by 2 years (i.e., excluding use in the prior 2 years at each time point during follow-up) were conducted to examine the extent to which the timing of metformin exposure might influence lung cancer risk. Because insulin and sulfonylureas have been previously reported to alter cancer risk, the choice of the reference (nonexposed) group may also affect risk estimates. To address this concern, sensitivity analyses were conducted separately among non-insulin users and among users of sulfonylureas only at baseline. These respective analyses permitted direct comparisons of patients who used metformin to patients who used other non-

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insulin medications and of patients who switched from using sulfonylureas to metformin to patients who used sulfonylureas only. In addition, subgroup analyses were conducted to explore whether risk associated with metformin use differed by gender, smoking status (current, former, never), tumor histology (adenocarcinoma, squamous cell, and small cell), and tumor stage (local, regional, and distant).

Results

In total, 47,351 patients met the study eligibility criteria. Within the 2 years before the start of follow-up, 51.4% had used sulfonylureas, 30.2% had used insulin, <0.1% had used other oral agents, and 24.7% had been on dietary therapy only. During 428,557 person-years of follow-up [mean (SD) = 9.0 (5.3) years], 747 patients were diagnosed with lung cancer.

Metformin users were generally younger at baseline than nonusers [mean (SD): 59.3 (10.1) vs. 65.0 (11.5) years], with more than 60% initiating metformin use within the first 4 years of follow-up (Table 1). Users were more commonly female and never smokers and less commonly non-Hispanic white than nonusers. On average, users also had higher glycated HbA1c levels, slightly higher BMI, a shorter duration of diabetes, and lower comorbidity index scores than nonusers.

Accounting for these and other potential confounding factors, ever use of metformin was not associated with overall lung cancer risk (Table 2; HR, 1.02; 95% CI, 0.85–1.22). Likewise, no clear associations were found with total duration, recency of use, or cumulative dose. Results from sensitivity analyses restricted to sulfonylurea users or non-insulin users at baseline and those lagging metformin use by 2 years were also not materially different (Supplementary Table S1).

When stratifying by baseline smoking status, however, ever use of metformin was associated with a decrease in risk among never smokers (Table 3; HR, 0.57; 95% CI, 0.33–0.99). Despite the limited number of metformin users diagnosed with lung cancer in this subgroup, risk appeared to decrease monotonically with longer duration of use, although not with greater cumulative dose. The decrease in risk associated with current use for ≥5 years (HR, 0.54; 95% CI 0.22–1.35) was comparable with that associated with any use for ≥5 years (HR, 0.48; 95% CI 0.21–1.09), albeit the decrease in risk associated with current use for <5 years was more pronounced (HR, 0.34; 95% CI 0.14–0.81). Among current smokers, corresponding risk estimates associated with metformin use were in the opposite direction (i.e., HRs >1.0), but none attained statistical significance. Among former smokers, associations between metformin use and lung cancer risk were generally null.

Results for subgroup analyses by histology were consistent with findings observed for subgroups based on smoking history (Table 4). Greater cumulative use of metformin was suggestively associated with lower risk of adenocarcinoma, the histology diagnosed most frequently in never smokers, yet higher risk of small cell carcinoma, the histology diagnosed almost exclusively in smokers. Patients who used metformin for ≥5 years, relative to never users, appeared less likely to develop adenocarcinoma (HR, 0.69; 95% CI, 0.40–1.17), but more likely to develop small cell carcinoma (HR, 1.82; 95% CI, 0.85–3.91). Risk estimates for current use for ≥5 years were generally comparable with those for any use for ≥5 years for each histologic type, although recent use was associated with increased risk of small cell carcinoma (HR, 2.29; 95% CI, 1.03–5.07), compared with never use. When comparing those who took the highest cumulative doses of metformin to never users, associations in opposite directions were similarly observed for risk of adenocarcinoma (HR, 0.61; 95% CI, 0.28–1.30) and small cell carcinoma (HR, 3.11; 95% CI, 1.22–7.95), although

Table 1. Baseline characteristics of 47,351 patients with diabetes

	Ever user *n* = 21,526 (45.5%) *n* (%)	**Never user *n* = 25,825 (54.5%) *n* (%)**
Age, y		
40–49	4,228 (19.6)	3,023 (11.7)
50–59	6,801 (31.6)	4,968 (19.2)
60–69	6,831 (31.7)	7,755 (30.0)
70+	3,666 (17.0)	10,079 (39.0)
Sex		
Male	11,256 (52.3)	14,292 (55.3)
Female	10,270 (47.7)	11,533 (44.7)
Race/ethnicity		
Non-Hispanic white	10,750 (49.9)	14,289 (55.3)
Black	2,420 (11.2)	3,335 (12.9)
Asian or Pacific Islander	3,173 (14.7)	2,358 (9.1)
Hispanic	2,921 (13.6)	2,543 (9.8)
Other	580 (2.7)	745 (2.9)
Missing	1,682 (7.8)	2,555 (9.9)
Median household income		
Low	10,092 (46.9)	13,010 (50.4)
High	11,134 (51.7)	11,975 (46.4)
Missing	300 (1.4)	840 (3.2)
Education level		
Less than high school	2,553 (11.9)	3,990 (15.5)
High school graduate	4,954 (23.0)	6,020 (23.3)
Some college	5,775 (26.8)	6,201 (24.0)
College graduate	2,294 (10.7)	2,220 (8.6)
Post-graduate	2,466 (11.5)	2,684 (10.4)
Missing	3,484 (16.2)	4,710 (18.2)
Smoking history		
Never	9,013 (41.9)	9,470 (36.7)
Former	6,949 (32.3)	8,995 (34.8)
Current	2,031 (9.4)	2,438 (9.4)
Missing	3,533 (16.4)	4,922 (19.1)
Alcohol history		
Never	3,638 (16.9)	4,255 (16.5)
Former	4,439 (20.6)	5,958 (23.1)
Current	9,557 (44.4)	10,179 (39.4)
Missing	3,892 (18.1)	5,433 (21.0)
HbA1c (%)		
<7	4,467 (20.8)	7,502 (29.0)
7–7.9	4,354 (20.2)	5,199 (20.1)
8–8.9	3,202 (14.9)	3,279 (12.7)
9–9.9	2,267 (10.5)	2,075 (8.0)
10+	3,975 (18.5)	2,978 (11.5)
Missing	3,261 (15.1)	4,792 (18.6)
BMI, kg/m^2[a]	29.7 (26.3–34.2)	27.9 (24.8–31.9)
Creatinine[a]	0.8 (0.7–1.0)	1.0 (0.8–1.3)
Time since diabetes diagnosis, (y)[a]	6.0 (3.0–11.0)	11.0 (5.0–19.0)
Charlson comorbidity index		
1	15,017 (69.8)	14,569 (56.4)
2	5,301 (24.6)	6,754 (26.2)
3+	1,208 (5.6)	4,502 (17.4)
Time since initiation of metformin (months)		
<12	3,560 (16.5)	
12–23	3,485 (16.2)	
24–35	3,385 (15.7)	
36–47	3,088 (14.4)	
48+	8,008 (37.2)	

[a]Median (interquartile range).

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Table 2. Estimates of lung cancer risk associated with metformin use

Metformin use	Number of events	Person-years	Adjusted[a] HR (95% CI)
Never	464	257,542.42	1.00 (reference)
Ever	283	171,015.06	1.02 (0.85–1.22)
Total duration, y			
<2.0	100	61,047.00	1.02 (0.81–1.28)
2.0–4.9	93	56,423.33	1.00 (0.78–1.28)
≥5.0	90	53,544.73	1.04 (0.78–1.37)
Recency of use			
Former	75	33,496.72	1.19 (0.89–1.58)
Recent	37	21,484.37	1.07 (0.75–1.52)
Current			
<5.0 years	107	75,365.20	0.93 (0.74–1.17)
≥5.0 years	64	40,668.76	1.04 (0.76–1.42)
Cumulative dose (mg), quartiles			
≤750,000	91	55,360.21	1.00 (0.79–1.27)
750,001–2,300,000	84	52,118.33	0.98 (0.76–1.27)
2,300,001–4,930,000	67	41,097.81	1.04 (0.77–1.39)
>4,930,000	41	22,438.70	1.21 (0.83–1.77)

[a]Stratified on age and adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, smoking history (status and pack-years), education, income level, creatinine level, HbA1c level, and use of other diabetes medications.

dose–response patterns were not monotonic. There was no clear evidence to suggest that the association between metformin use and lung cancer risk differed by gender or tumor stage (Supplementary Tables S2 and S3).

Discussion

Consistent with our prior research (15), we found no association between ever use of metformin and overall lung cancer risk in patients with diabetes. We also found no evidence of an association with total duration of use, recency of use, or cumulative dose. However, we noted suggestive, but intriguing differences in risk associated with metformin use between subgroups defined by smoking history and tumor histology.

As with all observational studies, our findings should be interpreted in the context of inherent limitations. Given our inability to differentiate patients with type II versus type I diabetes, eligibility was restricted to patients ≥40 years of age, when the vast majority of diabetes is type II. Use of metformin and other diabetes medications was determined solely from filled prescription records, and no data on medication adherence were collected. However, exposure misclassification was minimized by requiring two or more prescriptions of a given medication to have been filled within a 6-month period, and recall bias was avoided by using electronic pharmacy records. Although a fairly large cohort of patients with diabetes was followed over a 15-year period, the number of metformin users who developed lung cancer was still limited. This constraint reduced the precision of risk estimates, particularly in subgroup analyses. Also, although risk estimates were adjusted for a number of potential confounding variables, including BMI, smoking status, and pack-years smoked, these variables were assessed only once (i.e., before baseline), and residual confounding may still exist due to incompletely measured or unmeasured variables.

Our primary findings are compatible with those of two case–control studies conducted using the U.K. General Practice Research Database. Bodmer and colleagues (8) found no evidence of an inverse association between long-term metformin use (≥40

Table 3. Estimates of lung cancer risk associated with metformin use, by smoking status

	Never smoker			Former smoker			Current smoker			
Metformin use	Number of events	Person-years	Adjusted[a] HR (95% CI)	Number of events	Person-years	Adjusted[a] HR (95% CI)	Number of events	Person-years	Adjusted[a] HR (95% CI)	$P_{interaction}$[b]
Never	51	103,651.05	1.00 (reference)	222	84,763.54	1.00 (reference)	112	21,977.45	1.00 (reference)	
Ever	29	73,907.55	0.57 (0.33–0.99)	114	54,161.75	0.93 (0.71–1.23)	91	15,298.80	1.25 (0.88–1.77)	0.11
Total duration, y										
<2.0	10	25,648.96	0.66 (0.32–1.33)	38	19,466.59	0.88 (0.61–1.27)	35	5,792.32	1.38 (0.91–2.09)	
2.0–4.9	9	24,315.93	0.56 (0.26–1.20)	41	17,936.27	1.00 (0.69–1.45)	24	5,037.57	0.96 (0.58–1.57)	
≥5.0	10	23,942.66	0.48 (0.21–1.09)	35	16,758.89	0.93 (0.61–1.44)	32	4,468.91	1.45 (0.87–2.43)	0.35
Recency of use										
Former	9	14,007.31	0.79 (0.35–1.80)	29	11,092.11	1.00 (0.64–1.56)	21	3,083.62	1.15 (0.66–2.00)	
Recent	7	9,251.23	1.10 (0.47–2.56)	16	6,584.15	1.05 (0.62–1.78)	12	2,054.41	1.30 (0.69–2.46)	
Current										
<5.0 years	6	32,290.55	0.34 (0.14–0.81)	44	23,924.57	0.87 (0.61–1.23)	36	6,833.89	1.24 (0.82–1.89)	
≥5.0 years	7	18,358.46	0.54 (0.22–1.35)	25	12,560.92	0.93 (0.58–1.50)	22	3,326.87	1.39 (0.79–2.44)	0.35
Cumulative dose (mg), quartiles										
≤750,000	8	23,566.03	0.56 (0.26–1.22)	37	17,291.58	0.92 (0.64–1.32)	31	5,194.28	1.34 (0.87–2.06)	
750,001–2,300,000	10	22,464.73	0.67 (0.32–1.39)	35	16,423.18	0.93 (0.63–1.37)	22	4,567.76	0.99 (0.60–1.64)	
2,300,001–4,930,000	5	17,918.09	0.38 (0.14–1.03)	23	13,135.99	0.82 (0.51–1.32)	26	3,596.58	1.50 (0.90–2.50)	
>4,930,000	6	9,958.71	0.72 (0.26–2.00)	19	7,311.01	1.26 (0.72–2.20)	12	1,940.18	1.35 (0.66–2.75)	0.46

[a]Stratified on age and adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, pack-year history (for former and current smokers), education, income level, creatinine level, HbA1c level, and use of other diabetes medications.
[b]On the basis of test for interaction between metformin use and smoking status (never, former, and current) on lung cancer risk.

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Table 4. Estimates of lung cancer risk associated with metformin use, by histologic type

	Adenocarcinoma		Squamous cell carcinoma		Small cell carcinoma	
Metformin use	**Number of events**	**Adjusted[a] HR (95% CI)**	**Number of events**	**Adjusted[a] HR (95% CI)**	**Number of events**	**Adjusted[a] HR (95% CI)**
Never	121	1.00 (reference)	88	1.00 (reference)	62	1.00 (reference)
Ever	80	0.88 (0.62–1.25)	52	1.09 (0.71–1.68)	36	1.23 (0.74–2.04)
Total duration, y						
<2.0	26	0.92 (0.59–1.45)	16	0.94 (0.54–1.66)	14	1.23 (0.66–2.29)
2.0–4.9	30	0.99 (0.63–1.54)	16	1.10 (0.60–2.01)	8	0.88 (0.39–1.98)
≥5.0	24	0.69 (0.40–1.17)	20	1.46 (0.76–2.79)	14	1.82 (0.85–3.91)
Recency of use						
Former	23	0.99 (0.59–1.67)	12	1.10 (0.54–2.23)	8	1.45 (0.61–3.40)
Recent	11	0.94 (0.49–1.79)	3	0.52 (0.16–1.69)	8	2.29 (1.03–5.07)
Current						
<5.0 years	31	0.93 (0.60–1.43)	23	1.17 (0.71–1.95)	11	0.84 (0.42–1.67)
≥5.0 years	15	0.61 (0.33–1.13)	14	1.30 (0.65–2.62)	9	1.58 (0.68–3.69)
Cumulative dose (mg), quartiles						
≤750,000	21	0.79 (0.49–1.28)	18	1.14 (0.66–1.95)	11	1.08 (0.55–2.14)
750,001–2,300,000	31	1.12 (0.72–1.74)	11	0.80 (0.41–1.58)	8	0.94 (0.42–2.09)
2,300,001–4,930,000	19	0.80 (0.46–1.39)	12	1.17 (0.58–2.37)	9	1.59 (0.70–3.61)
>4,930,000	9	0.61 (0.28–1.30)	11	2.03 (0.90–4.55)	8	3.11 (1.22–7.95)

[a]Stratified on age and adjusted for gender, race/ethnicity, birth year, diabetes duration, BMI, alcohol use, Charlson comorbidity index, smoking history (status and pack-years), education, income level, creatinine level, HbA1c level, and use of other diabetes medications.

prescriptions) and lung cancer risk (OR, 1.09; 95% CI, 0.85–1.38). Among patients with type II diabetes newly treated with oral hypoglycemic agents, Smiechowski and colleagues (11) similarly found no decrease in risk of lung cancer associated with increasing number of metformin prescriptions (≥46 prescriptions: OR, 1.00; 95% CI, 0.75–1.33), total duration, or cumulative dose. In both studies, time-window and time-lag biases were minimized by matching controls to cases on time of exposure assessment before the index (diagnosis) date and accounting for potential confounding by diabetes duration, respectively. Regression models were adjusted for BMI and smoking status (along with other potential confounders by Smiechowski and colleagues only), although not for pack-years smoked. In contrast, others have found striking reductions in risk associated with metformin use of up to 52%, likely from failing to account for time-related biases (10, 13, 14).

To avoid immortal time and time-lag biases, we examined metformin and other diabetes medications as time-dependent exposures and controlled for diabetes duration and HbA1c level (as a proxy for severity) in our cohort analyses. However, diabetes duration did not appear to be a strong confounder in our study population, consistent with prior evidence that KPNC patients with diabetes are not at altered risk for lung cancer (23). We evaluated only new use of metformin, although most metformin users had previously used sulfonylureas or insulin. To address concerns about the lack of a single comparator drug and the possible link between insulin use and increased lung cancer risk (8), we conducted sensitivity analyses comparing metformin users with either sulfonylurea-only users or other non-insulin drug users, which yielded similar results to our primary analyses.

We further explored whether lung cancer risk associated with metformin use differed by smoking history and tumor characteristics, which has been conducted in only a few other studies. Smiechowski and colleagues (11) found no clear difference in association for ever use of metformin by smoking history (never smokers: OR, 1.2; 95% CI, 0.62–2.26; ever smokers: OR, 0.90, 95% CI, 0.70–1.15), but their mean follow-up was shorter than ours (5.6 vs. 9.0 years). Because we observed a stronger inverse association with ≥5 year-duration of metformin use in never smokers, longer follow-up may be needed to detect this subgroup effect if it truly exists. Mazzone and colleagues (10) reported different patterns of metformin use by histologic subtype among patients with lung cancer. However, to our knowledge, our study is the first to suggest any variation in association by lung cancer histology, with metformin users (vs. nonusers) being less likely to develop adenocarcinoma, but more likely to develop small cell carcinoma.

Given lung cancer is an etiologically heterogeneous disease, such subgroup effects could exist, although biologic explanations for these differences are unknown and chance cannot be ruled out. It is also possible that among never smokers, metformin users used health care less often and were less likely to have lung cancer detected than nonusers, whereas among current smokers, metformin users used health care more often and were more likely to have lung cancer detected than nonusers. Yet, the proportion of localized disease in users than nonusers was fairly similar (i.e., 14% vs. 12%), suggesting minimal detection bias.

In conclusion, we found no evidence that metformin use affects overall risk of lung cancer in patients with diabetes. The suggested variation in the association by smoking history and lung cancer histology warrants confirmation (or refutation) by others. To the extent possible, future studies of metformin use and lung cancer risk should be conducted in larger, well-characterized cohorts of persons with diabetes over an extended period of follow-up, accounting for time-related and other potential biases.

Disclosure of Potential Conflicts of Interest

A. Ferrara reports receiving a commercial research grant from Takeda. L.A. Habel reports receiving a commercial research grant Takeda, Sanofi, and Genentech. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: L.C. Sakoda, A. Ferrara, L.A. Habel
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Ferrara, N.S. Achacoso, T. Peng, S.F. Ehrlich
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.C. Sakoda, N.S. Achacoso, C.P. Quesenberry Jr, L.A. Habel

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