INHALED INSULIN ASSESSMENT OF INCIDENT LUNG CANCER RISK AMONG ADULTS WITH TYPE 2 DIABETES (T2D) COMPARED TO OTHER THERAPIES USING REAL-WORLD EVIDENCE

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OBJECTIVE

- To evaluate the risk of incident lung cancer following exposure to inhaled insulin over an 8-year period
- To compare lung cancer incidence in inhaled insulin users with injectable rapid-acting insulin and other T2D treatment cohorts
- To utilize linked, national real-world claims and EMR data to assess long-term pulmonary safety

CONCLUSIONS

- No evidence of increased incident lung cancer risk was observed among inhaled insulin users in this large real-world cohort.
- Lung cancer incidence among inhaled insulin users was lower than or comparable to multiple T2D comparator cohorts.
- Findings support the pulmonary safety profile of inhaled insulin in routine clinical practice.

INTRODUCTION

Technosphere® Insulin is an ultra-rapid-acting inhaled insulin and the only inhaled insulin currently approved by the US Food and Drug Administration for improving glycemic control in adults with diabetes. Because inhaled insulin is administered via the pulmonary route, long-term lung safety has been an area of continued regulatory and clinical interest. To date, published literature and post-marketing surveillance have not identified an increased lung cancer risk associated with inhaled insulin use; however, available studies have been limited by sample size, duration of follow-up, or reliance on spontaneous adverse event reporting.

Real-world evidence (RWE) derived from large, longitudinal healthcare databases enables evaluation of safety outcomes under routine clinical conditions. This study leverages linked adjudicated claims and electronic medical record (EMR) data from a diverse US population to assess incident lung cancer risk among adults with type 2 diabetes (T2D) treated with inhaled insulin compared with injectable rapid-acting insulin and other commonly used diabetes therapies.

METHODS

Study Design and Data Sources

This retrospective cohort study used de-identified, closed health plan claims data linked to structured electronic medical record (EMR) data through secure tokenization. The study period spanned January 1, 2017 through August 31, 2025, with representation from commercial, Medicare Advantage, and managed Medicaid plans across all 50 U.S. states. Data linkage enabled longitudinal follow-up across care settings while preserving patient privacy.

Study Population

The source population comprised U.S. adults with evidence of type 2 diabetes (T2D) in claims or EMR data. Patients were required to have longitudinal observable data with ≥6 months of baseline activity prior to cohort entry and follow-up data after index (dx for no therapy group, start of therapy for by cohort). To ensure capture of incident outcomes and baseline covariates, patients were required to have continuous enrollment or clinical activity within the health system during the observation window.

Patients with evidence of primary lung cancer during the baseline period were excluded from incident lung cancer analyses. Patients were required to be ≥18 years of age at index. Individuals with diagnoses of type 1 diabetes, gestational diabetes, or secondary diabetes were excluded.

The primary comparison evaluated:
- Inhaled insulin
- Injectable rapid-acting insulin (RAA)

Contextual comparator cohorts included:
- No prescription therapy
- Oral agents
- GLP-1 agonists
- Long-acting insulins

For treated cohorts, time at risk began at initiation of the index therapy. For the no-therapy cohort, time at risk began at the date of T2D diagnosis. Follow-up continued until lung cancer diagnosis, disenrollment, death, or end of data availability.

The primary outcome was incident lung cancer, identified using ICD-10 diagnosis codes in adjudicated claims and supported by EMR abstraction.

Statistical Analysis

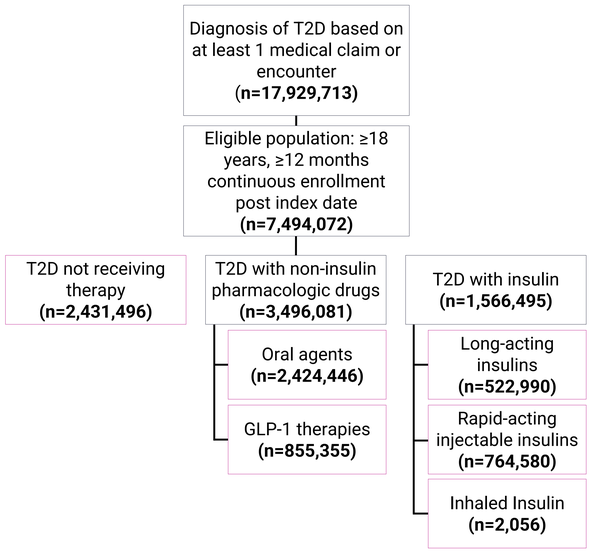
Incident lung cancer was summarized using incidence proportions across cohorts. Follow-up duration was described using mean time at risk. A multivariable Cox proportional hazards regression model was conducted to estimate relative risk while adjusting for demographic and clinical covariates, including age, sex, smoking-related diagnoses, and comorbidity burden. Adjusted analyses were used to contextualize descriptive findings.

RESULTS

Study Population

Among 17,929,713 adults diagnosed with T2D who were screened for inclusion, application of prespecified inclusion and exclusion criteria yielded 7,494,072 eligible patients with sufficient baseline and follow-up data and no evidence of primary lung cancer at cohort entry. Patients were distributed across six mutually exclusive treatment cohorts reflecting real-world antidiabetic therapy patterns. The inhaled insulin cohort included 2,056 and the rapid-acting insulin cohort included 764,580, **Figure 1**.

Figure 1. Cohort Diagram



Incident Lung Cancer

Among inhaled insulin users, 10 incident lung cancer events were identified, corresponding to an incidence of 1.46 per 1,000 patient-years. In the injectable rapid-acting insulin cohort, lung cancer incidence was 4.10 per 1,000 patient-years. Incidence in other comparator cohorts ranged from 1.29 to 3.48 per 1,000 patient-years, **Table 1**.

Given the low number of events in the inhaled insulin cohort, confidence intervals around incidence estimates were wider than those observed in larger comparator cohorts. However, the estimates remained centered near the null, and the observed ranges did not indicate a concerning elevation in lung cancer risk.

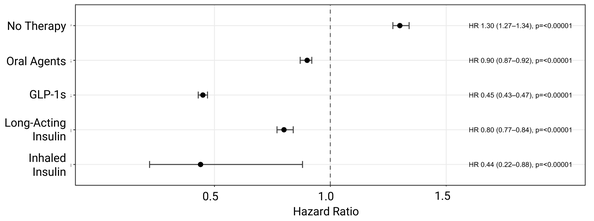
Adjusted Analyses

In multivariable Cox proportional hazards models, the hazard ratio for inhaled insulin compared with injectable rapid-acting insulin was not suggestive of increased lung cancer risk, **Figure 2**. As expected, given the limited number of outcome events, the confidence interval was wider than those for higher-exposure cohorts but remained centered around the null and overlapped unity, indicating no observed safety signal. Adjusted results were directionally consistent with unadjusted findings after accounting for demographics, smoking-related diagnoses, and comorbidity burden.

Table 1. Incidence of Primary Lung Cancer

T2D Cohort	N	Primary Lung Cancer Events (n)	Incidence per 1,000 PY (95% CI)
No Therapy	2,431,496	27,295	3.48 (3.44-3.52)
Oral Agents	2,424,446	19,531	2.37 (2.34-2.41)
GLP-1 Agonists	855,355	2,809	1.29 (1.25-1.34)
Long-Acting Insulins	521,685	4,003	2.26 (2.19-2.33)
Rapid-Acting Insulins	764,580	8,936	4.10 (4.02-4.19)
Inhaled Insulin	2,056	10	1.46 (0.70-2.68)

Figure 2. Multivariate Cox Regression Model Compared to Rapid-Acting Insulins in T2D



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