Inhaled Corticosteroids and Risk of Lung Cancer among Patients with Chronic Obstructive Pulmonary Disease

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***Rationale and Objectives*: Lung cancer is a frequent cause of death among patients with chronic obstructive pulmonary disease (COPD). We examined whether the use of inhaled corticosteroids among patients with COPD was associated with a decreased risk of lung cancer.**

***Methods*: We performed a cohort study of United States veterans enrolled in primary care clinics between December 1996 and May 2001. Participants had received treatment for, had an *International Classification of Disease, 9th edition*, diagnosis of, or a self-reported diagnosis of COPD. Patients with a history of lung cancer were excluded. To be exposed, patients must have been at least 80% adherent to inhaled corticosteroids. We used Cox regression models to estimate the risk of cancer and adjust for potential confounding factors.**

***Findings*: We identified 10,474 patients with a median follow-up of 3.8 years. In comparison to nonusers of inhaled corticosteroids, adjusting for age, smoking status, smoking intensity, previous history of non–lung cancer malignancy, coexisting illnesses, and bronchodilator use, there was a dose-dependent decreased risk of lung cancer associated with inhaled corticosteroids (ICS dose $< 1{,}200$ μg/d: adjusted HR, 1.3; 95% confidence interval, 0.67–1.90; ICS dose $\geq 1{,}200$ μg/d: adjusted HR, 0.39; 95% confidence interval, 0.16–0.96). Changes in cohort definitions had minimal effects on the estimated risk. Analyses examining confounding by indication suggest biases in the opposite direction of the described effects.**

***Interpretation*: Results suggest that inhaled corticosteroids may have a potential role in lung cancer prevention among patients with COPD. These initial findings require confirmation in separate and larger cohorts.**

Keywords: chronic obstructive pulmonary disease; pharmacoepidemiology; lung cancer; adherence

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Chronic obstructive pulmonary disease is a major risk factor for lung cancer. Both conditions are associated with inflammation and there are no therapies that have been demonstrated to be chemoprotective for lung cancer.

What This Study Adds to the Field

Inhaled corticosteroids used in clinical practice are associated with a decreased risk of lung cancer among patients with COPD.

Lung cancer is the most common cause of cancer related death in the United States, and accounts for more deaths each year than breast, prostate, and colorectal cancer combined (1). Studies such as the Lung Health Study have demonstrated that the most common cause of death among subjects with chronic obstructive pulmonary disease (COPD) is lung cancer (2–4). From a public health perspective, the effort to reduce the morbidity and mortality associated with lung cancer is a priority that has been difficult to address. The marked reduction in the prevalence of smoking due to public health interventions may protect those without prior significant smoke exposure, but does little for those at high risk from current or even past heavy smoking (5). Potential interventions for reducing death and disease among those who are at high risk of lung cancer have focused on the early detection and treatment of lung cancer or cancer prevention (6–12). However, although debated (13), screening for lung cancer has been suggested to be ineffective at reducing morbidity or mortality, and preventative measures have resulted in few successes (14–18). Smoking cessation/reduction and observational studies of dietary intake of phytoestrogens represent the only studies that have been associated with a decreased risk for lung cancer (4, 19–21).

A portion of the well-described link between COPD and lung cancer (22) is in part related to common exposure to tobacco smoke (23, 24); however, for any level of tobacco exposure, patients with COPD have a greater risk factor for lung cancer than smokers without COPD (25). Tobacco smoke is a well-recognized stimulant of systemic and local inflammation and the role of inflammation in the causal pathway for both lung cancer and COPD has been suggested (26). Previous studies have demonstrated that inhaled corticosteroids (ICS) reduce local and systemic inflammation among patients with COPD (27, 28), and animal models have demonstrated that glucocorticoids inhibit growth of lung cancer cells (29, 30). On the basis of this information, we sought to examine the association between ICS and risk of lung cancer among patients with COPD. Our *a priori* hypothesis was that ICS would be associated with a reduced risk of lung cancer among patients with COPD. A portion of this

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study was presented at the 2006 American Thoracic Society International Conference (31).

METHODS

Design and Subjects

We performed a cohort study using data prospectively collected for the Veterans Affairs (VA)–funded Ambulatory Care Quality Improvement Project (ACQUIP) (32). The ACQUIP was a multicenter randomized trial that had no documented effect, but sought to assess whether monitoring patients' self-reported health with provision of regular reports to primary care physicians improved patients' health status and satisfaction with care. The ACQUIP sought to enroll all patients actively participating in the General Internal Medicine clinics of seven VA medical centers nationwide: VA Puget Sound Health Care System in Seattle, Washington; West Los Angeles, California; Birmingham, Alabama; Little Rock, Arkansas; San Francisco, California; Richmond, Virginia; and White River Junction, Vermont. This study was approved by the institutional review board (IRB) of the University of Washington.

We included patients who were enrolled in ACQUIP between December 1996 and October 1999. Subjects who returned the health inventory checklist had at least one visit to the General Internal Medicine clinic and had at least one of the following: (*1*) an *International Classification of Diseases*, *9th revision* (ICD-9)–coded diagnosis consistent with COPD (ICD-9: 496.x, 493.2), (*2*) a self-report of chronic lung disease, or (*3*) prescriptions filled for bronchodilators (β_2-agonists or anticholinergics) in the 12 months before their enrollment date. Patients younger than 40 years or who had an ICD-9 code diagnosis of lung cancer before the index date were excluded from the analyses.

Data Collection

As part of the ACQUIP, baseline assessment of coexisting conditions was obtained by mailed survey. The baseline health inventory inquired about the presence of 24 chronic conditions, including chronic lung disease, ischemic heart disease, and tobacco use. In addition, weekly interrogations of the VA computerized medical record system were performed to determine inpatient and outpatient visits. Data on exposures and covariates were determined at the time of enrollment to the study, defined as the day that a patient's health inventory was processed (index date). Outpatient pharmacy records, which were collected from each site as part of the ACQUIP protocol for all subjects, were obtained and used to ascertain exposure to ICS.

Exposure and Outcome of Interest

Subjects were considered exposed to ICS if they had filled sufficient medication to be at least 80% adherent during the 180 days before their index date. Adherence was estimated using a modification of methods described by Steiner that accounts for medications received before the exposure period (33). The ICS on formulary during this period included triamcinolone, beclomethasone, flunisolide, and fluticasone. All ICS preparations were converted to triamcinolone dose equivalents (2× beclomethasone, 1× flunisolide, and 4× fluticasone) (34). An average daily dose was calculated by dividing the total number of micrograms (based on canisters dispensed) by the number of days prescribed during the assessment period. Inhaled corticosteroid dose was assessed as both a continuous and a categorical variable.

The outcome of interest was a primary inpatient or outpatient ICD-9 diagnosis of lung cancer (162.x or 163.x) that occurred after the date of enrollment. Previously published results suggest a high degree of concordance between an ICD-9 lung cancer diagnosis and diagnosis obtained by chart abstraction from medical records review (35). In addition, we abstracted charts for 50 randomly selected patients seen at the VA Puget Sound who had an ICD-9 diagnosis of lung cancer (162.x or 163.x) in Calendar Year 2004, but who did not have a diagnosis in Calendar Year 2003. Of these 50 patients, 46 (92%) had a histologically confirmed diagnosis of lung cancer or had an enlarging chest mass consistent with lung cancer. Two had previously resected lung cancer and were being seen for follow-up. One patient had a sarcoma that had metastasized to the chest and one patient had tuberculosis diagnosed at resection of the nodule. No patient was being seen for interval chest imaging of an undiagnosed pulmonary nodule.

Covariate Definitions

We adjusted for overall comorbidity using the Seattle Index of Comorbidity (SIC), a validated risk adjustment score that predicts mortality and resource utilization (36). The SIC is a weighted score derived from self-report of conditions and incorporates history of previous myocardial infarction, cancer, chronic lung disease, chronic heart failure, pneumonia, cerebral vascular accidents, and smoking status.

Smoking status was obtained by self-report and categorized as never, past, and current smoker. Smoking intensity was described as cigarettes per day and was modeled as a continuous variable. Alcohol consumption was estimated using the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) questions (37). We obtained sociodemographic characteristics, including race and educational achievement, by self-report and estimated travel burden to the VA center by calculating the straight-line distance from the centroid of the zip code of the subject and his or her respective medical center (38). As a proxy of COPD severity, we assessed the number of canisters of ipratropium bromide and β-agonists prescribed during the 6 months before the index date.

Statistical Methods

All statistical analyses were performed using Stata 8.0 (StataCorp, College Station, TX). All statistical tests were two-tailed, and p values less than 0.05 were considered statistically significant. Bivariate Pearson's χ^2 tests were used for bivariate analyses comparing the characteristics of those subjects who were exposed or unexposed to ICS. A Cox proportional hazard model was used to estimate the risk of lung cancer development and adjust for potential confounding factors. Subjects were censored at death. Potential confounding variables were entered individually and *en bloc*. The proportional hazard assumption was tested using Schoenfeld residuals. To assess the potential for effects of bias by indication, we also developed a propensity score using logistic regression by calculating the probability of currently using ICS and stratifying the cohort into quintiles based on the propensity score to ensure balance of propensity scores between covariates and ICS (39).

RESULTS

We identified 10,474 subjects who met our eligibility criteria. The cohort had a median follow-up time of 3.84 years (interquartile range, 2.08–4.29 yr) and a maximum follow-up time of 4.6 years. Patient characteristics are summarized in Table 1. Consistent with VA populations, the majority of the cohort were older white men with a significant number of coexisting illnesses. Although 20% of the cohort had received ICS in the 180 days before the index date, only 5% of the cohort were at least 80% adherent to an inhaled corticosteroid. Subjects that had filled ICS had a tendency to be older, had slightly lower comorbidity index scores, were more likely to be white, and were more likely to be ex-smokers, but had similar intensity of tobacco exposure. Subjects who were exposed to ICS were also more likely to have filled a greater number of β-agonist canisters and were more likely to have filled prescriptions for ipratropium bromide.

ICS and Lung Cancer Risk

During the follow-up period, 423 (4.0%) patients had a new ICD-9 diagnosis of lung cancer at a median of 1.4 years (interquartile range, 0.7–2.5 yr) after the index date. The mean daily dose of ICS in triamcinalone equivalents was not statistically different among patients who did not develop lung cancer (mean ICS dose among patients with lung cancer was 910.2 μg [± 449.54]; ICS dose among patients without lung cancer was 1,115.9 μg [± 619.40; p = 0.13]). After adjusting for confounding factors, including age, smoking status, and intensity, previous history of non–lung and non–skin cancer, comorbidity, and bronchodilator use, there was a trend toward reduction in lung cancer risk for each 100 μg of triamcinalone equivalents (Table 2) (adjusted hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.93–1.00; p = 0.083). Adjusting for propensity of receiving an inhaled corticosteroid did not

TABLE 1. PATIENT CHARACTERISTICS

Characteristics	Cohort (*n* = *10,474*) ICS Users (*n* = *517*)	No ICS (*n* = *9,957*)	p Value
Age, mean, yr (SD)	66 (10)	64 (11)	< 0.001
Male, %	97	97	0.68
White, %	85	76	< 0.001
SIC score, mean (SD)	4.6 (0.09)	4.8 (0.02)	0.027
Miles to medical center, mean (SD)	58.5 (165)	50.4 (135)	0.19
Graduated high school, %	37.8	35.1	0.23
AUDIT-C score, mean (SD)	1.6 (2.45)	1.9 (2.87)	0.017
Smoking status, *n* (%)			
Never	47 (9)	1,204 (12)	
Former	341 (68)	5,188 (53)	
Current	117 (23)	3,349 (35)	< 0.001
Smoking intensity (cigarettes/d)			
None	47 (9)	1,204 (13)	
< 10	56 (11)	1,299 (14)	
11–15	63 (13)	1,178 (12)	
16–20	110 (22)	2,133 (22)	
21–30	104 (22)	1,760 (18)	
31–40	71 (14)	1,033 (11)	
> 40	47 (9)	928 (10)	0.052
History of non–skin malignancy, *n* (%)	69 (13)	1,320 (13)	0.96
β-Agonist use (canisters/mo)			
0	123 (24)	8,344 (84)	
1–3	311 (60)	1462 (15)	
> 3	83 (16)	151 (1)	< 0.001
Ipratropium bromide, *n* (%)	348 (67)	2,767 (28)	< 0.001

Definition of abbreviations: AUDIT-C = Alcohol Use Disorders Identification Test–Consumption questions; ICS = inhaled corticosteroids; SIC = Seattle Index of Comorbidity.

significantly change the trend toward reduction in lung cancer risk (adjusted HR, 0.96; 95% CI, 0.92–1.00; p = 0.075).

A priori, we stratified inhaled corticosteroid use into two groups to ensure roughly equal number of subjects in each stratum: less than 1,200 μg or 1,200 μg or more triamcinalone equivalents per day. Unadjusted analysis demonstrated a non–statistically significant dose–response association between ICS and lung cancer (Table 2) (ICS dose < 1,200 μg/d: adjusted HR, 1.36; 95% CI, 0.83–2.25; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.56; 95% CI, 0.23–1.36). After adjusting for age, smoking status, smoking intensity, previous history of non–lung and non–skin cancers, comorbidity, and bronchodilator use, the dose–response relationship persisted (ICS dose < 1,200 μg/d: adjusted HR, 1.13; 95% CI, 0.67–1.90; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.39; 95% CI, 0.16–0.96). The relationship between potential confounding variables and risk of lung cancer from the adjusted model (Figure 1) demonstrates expected increased risk among factors known to be associated with lung cancer development, including age, current and former smoker, smoking intensity, previous cancers, and nonsignificant trends in bronchodilator use (marker of COPD severity). Adjusting for the propensity of receiving ICS had a modest effect on the overall results (ICS dose < 1,200 μg/d: adjusted HR, 1.35; 95% CI, 0.82–2.23; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.57; 95% CI, 0.24–1.38). The addition of sociodemographic characteristics, AUDIT-C score, and distance to the VA medical center had minimal effects on the estimated risk when either added alone or *en bloc* (ICS dose < 1,200 μg/d: adjusted *en bloc* HR, 1.06; 95% CI, 0.62–1.86; ICS dose ⩾ 1,200 μg/d: adjusted *en bloc* HR, 0.45; 95% CI, 0.18–1.11). Adjusting for coexisting illnesses individually did not affect the point estimates (ICS dose < 1,200 μg/d: adjusted HR, 1.13; 95% CI, 0.67–1.90; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.40; 95% CI, 0.16–0.98). In addition, we tested whether nonwhite individuals had differential effects of ICS on lung cancer risk. We found the described effect was similar in direction for both whites (ICS dose < 1,200 μg/d: adjusted *en bloc* HR, 1.15; 95% CI, 0.66–2.00; ICS dose ⩾ 1,200 μg/d: adjusted *en bloc* HR, 0.40; 95% CI, 0.15–1.07) and nonwhites (ICS dose < 1,200 μg/d: adjusted *en bloc* HR, 1.08; 95% CI, 0.25–4.61; ICS dose ⩾ 1,200 μg/d: adjusted *en bloc* HR, 0.68; 95% CI, 0.09–5.24). Testing for effect modification by race was not statistically significant (p = 0.10).

Risk of Lung Cancer Restricted to Subjects with More than 1 Year of Follow-up

Although we had selected the cohort based on never having had a prior diagnosis of lung cancer, we excluded the subjects who had a lung cancer diagnosis in the first year after the index date. This restriction reduced the total number of patients who had experienced lung cancer to 254 subjects. Performing the same analyses as described above, after adjusting for confounding factors including age, smoking status and intensity, previous history of non–lung and non–skin cancer, comorbidity, and bronchodilator use, there was a non–statistically significant reduction in lung cancer risk for each 100 μg of triamcinalone equivalents (adjusted HR, 0.96; 95% CI, 0.91–1.01). Similarly, when stratified by dose, the point estimate at the higher dose of ICS remained essentially unchanged. (ICS dose < 1,200 μg/d: adjusted HR, 0.85; 95% CI, 0.39–1.84; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.41; 95% CI, 0.13–1.31)

Risk of Lung Cancer among Only Users of ICS

We performed secondary analyses to examine the effect of ICS on lung cancer risk, restricting analyses to those 517 subjects

TABLE 2. RISK OF LUNG CANCER DEVELOPMENT BASED ON THE DOSE OF INHALED CORTICOSTEROIDS

Triamcinalone Equivalents	Person-Years at Risk	Total (*n* = *10,474*)	Lung Cancer (*n* = *423*)	Unadjusted HR (*95% CI*)	Adjusted HR* (*95% CI*)
Continuous					
Per 100 μg/d	33,436	10,474	423	0.98 (0.95–1.02)	0.96 (0.93–1.00)
Categorical					
Nonusers	31,799	9,957	402	Referent	Referent
< 1,200 (μg/d)	928	298	16	1.36 (0.83–2.25)	1.13 (0.67–1.90)
⩾ 1,200 (μg/d)	709	219	5	0.56 (0.23–1.36)	0.39 (0.16–0.96)

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; ICS = inhaled corticosteroids.

* Adjusted for age, smoking status and smoking intensity, history of malignancy other than skin cancer, Seattle Index of Comorbidity score, and bronchodilator use.

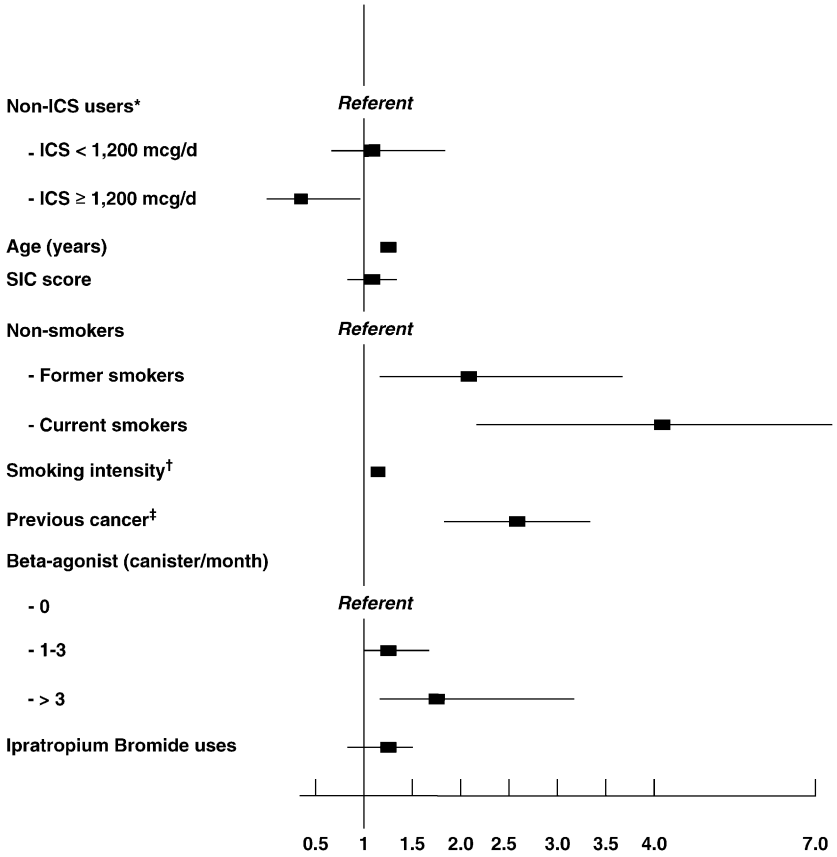

Figure 1. Adjusted risk of lung cancer development among chronic obstructive pulmonary disease cohort. ICS = inhaled corticosteroids; SIC = Seattle Index of Comorbidity. *Dose presented as micrograms per day; †smoking intensity was defined as risk per 10 cigarettes/day; ‡previous history of cancer other than skin cancer.

who had been adherent to ICS. In unadjusted analysis, for each 100-μg triamincalone-equivalent increase, there was a similar dose–response decrease in risk of lung cancer (HR, 0.93; 95% CI, 0.85–1.01). This effect persisted after adjustment for smoking status and intensity, age, history of non–skin and non–lung cancer, comorbidity, and bronchodilator use (adjusted HR, 0.90; 95% CI, 0.82–0.99).

Assessment of Cohort Definition

To assess for any potential effects of misclassification caused by our cohort definition, we performed analyses using a series of cohorts defined by increasingly restrictive criteria that were designed to exclude subjects with nonspecific symptoms or asthma (Table 3). Regardless of the stringency of the restrictive criteria, the point estimates did not change appreciably. For example, restricting our analysis to only those subjects who had self-reported COPD, an ICD-9 diagnosis of COPD, and filled bronchodilators in the previous 12 months, we found the adjusted risk of lung cancer associated with ICS was largely unchanged (ICS dose < 1,200 μg/d: adjusted HR, 0.98; 95% CI, 0.54–1.80; ICS dose ⩾ 1,200 μg/d: adjusted HR, 0.44; 95% CI, 0.18–1.09). Similarly, for those subjects who had an ICD-9 code for COPD and prescriptions for ipratropium bromide, the adjusted risk was 1.09 (95% CI, 0.55–2.19) for those who filled their bronchodilators with less than 1,200 μg/day and 0.37 (95% CI, 0.13–1.01) for those who filled their bronchodilators with 1,200 μg/day or more.

TABLE 3. ADJUSTED* RISK OF LUNG CANCER DEVELOPMENT BASED ON COHORT DEFINITIONS STRATIFIED BY INHALED CORTICOSTEROID DOSES

	Cohort Definitions†				
ICS Dose (μg/d)	A (*n* = 6,128)	B (*n* = 4,016)	C (*n* = 4,055)	D (*n* = 2,493)	E (*n* = 3,233)
Nonusers	Referent	Referent	Referent	Referent	Referent
< 1,200	1.01 (0.57–0.80)	0.97 (0.54–1.78)	0.95 (0.53–1.73)	1.09 (0.55–2.19)	0.98 (0.54–1.80)
⩾ 1,200	0.41 (0.17–1.02)	0.44 (0.18–1.03)	0.40 (0.16–0.99)	0.37 (0.13–1.01)	0.44 (0.18–1.09)

Definition of abbreviation: ICS = inhaled corticosteroids.

* Adjusted for age, smoking status and smoking intensity, history of malignancy other than skin cancer, Seattle Index of Comorbidity score, and bronchodilator use.

† Cohort definitions: A = cohort defined based on COPD ICD-9 code; B = cohort defined based on COPD ICD-9 code and self-report of "chronic lung disease, emphysema, asthma, or bronchitis"; C = cohort defined based on COPD ICD-9 code and bronchodilator (β-agonist metered-dose or nebulizer, oral bronchodilators, or ipratropium bromide) uses; D = cohort defined based on COPD ICD-9 code and ipratropium bromide uses; E = cohort defined based on COPD ICD-9 code and self-report of "chronic lung disease, emphysema, asthma, or bronchitis" and bronchodilator (β-agonist metered-dose or nebulizer, oral bronchodilators, or ipratropium bromide) use.

TABLE 4. RISK OF LUNG CANCER DEVELOPMENT STRATIFIED BY SMOKING STATUS

ICS Doses	Person-Years at Risk	Total (*n*)	Lung Cancer (*n*)	Adjusted HR* (*95% CI*)
Former smokers				
Continuous variable (per 100 μg/d)	17,610	5,529	225	0.97 (0.92–1.02)
Categorical variables				
Nonusers	16,551	5,188	211	Referent
< 1,200 μg/d	624	201	11	1.22 (0.65–2.30)
⩾ 1,200 μg/d	434	140	3	0.41 (0.13–1.30)
Current smokers (per 100 μg/d)				
Continuous variable	10,952	3,466	174	0.96 (0.89–1.03)
Categorical variables				
Nonusers	10,573	3,349	168	Referent
< 1,200 μg/d	202	64	4	1.01 (0.36–2.81)
⩾ 1,200 μg/d	176	53	2	0.39 (0.10–1.64)

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; ICS = inhaled corticosteroids.

* Adjusted for age, smoking status and smoking intensity, history of malignancy other than skin cancer, Seattle Index of Comorbidity score, and bronchodilator use.

Effects of Tobacco Use and Confounding by Indication for Symptoms of Lung Cancer

To assess the potential effects of tobacco exposure, we repeated the analysis after stratifying the cohort according to smoking status (Table 4). After adjustment for age, smoking intensity, history of non–lung and non–skin cancer, comorbidity, and bronchodilator use, the estimated risks for former and current smokers were similar to those observed in previous analyses. As an assessment of confounding by indication for symptoms associated with lung cancer, we examined the association of inhaled corticosteroid use among patients who were excluded from the above analyses because of a previous diagnosis of lung cancer. As expected, there was a strong dose–response relationship in the opposite direction of the results noted above (Table 5) (ICS dose < 1,200 μg/d: adjusted HR, 1.25; 95% CI, 0.63–2.47; ICS dose ⩾ 1,200 μg/d: adjusted HR, 4.67; 95% CI, 1.06–20.53).

DISCUSSION

Long-term follow-up of the Lung Health Study and others have demonstrated lung cancer is among the most common cause of death among subjects with COPD (2–4). ICS are currently recommended for patients with moderate to severe COPD, who are also the individuals at highest risk for developing lung cancer (22, 24, 25, 40). There have been multiple randomized control trials of ICS either alone (2, 3, 41, 42) or in combination with long-acting β-agonists among patients with COPD (43–46). However, none of these trials were designed or powered to demonstrate the effects of ICS on cancer risk. Recently, secondary data analysis of pooled primary data from these clinical trials demonstrated a non–statistically significant reduction in cancer-related mortality among those subjects randomized to ICS (47). The majority of these cancers were reported to be of the lung (47). Among individuals with a high likelihood of having COPD, we found that higher doses of ICS were associated with a decreased risk of lung cancer. If confirmed by others, our study has potentially important implications for lung cancer pathogenesis and chemoprevention.

Tobacco smoke is a potent stimulant of both innate and adaptive inflammatory response. In COPD, chronic inflammation has been suggested to contribute to COPD pathogenesis (40, 48). The inflammatory response to tobacco smoke appears to be greater among people who are susceptible to developing COPD (49, 50), and, among patients with COPD, airway and systemic inflammation appears to persist long after successful smoking cessation (51–54). Chronic inflammation has also been implicated in the pathogenesis of a number of cancers (55–57). Exposure to *Chlamydia pneumoniae*, which can chronically stimulate the innate immune system to release inflammatory mediators such as tumor necrosis factor-α, IL-1β, and IL-8 (58), has been associated with an increased risk for lung cancer (59–63). In lieu of the accumulating evidence implicating the role of inflammation in lung cancer pathogenesis (64, 65), it is plausible that chronic inflammation within the lung may result in repeated injury and repair that lead to a high rate of cell turnover, propagation of genetic errors, and ultimately, development of lung cancer (66).

ICS have been shown in prospective studies to suppress systemic markers of inflammation, such as C-reactive protein (67,

TABLE 5. RISK OF BEING EXPOSED TO INHALED CORTICOSTEROIDS AMONG PATIENTS WITH A HISTORY OF PREVIOUS LUNG CANCER

ICS Doses	Person-Years at Risk	Total (*n = 494*) (%)	Unadjusted HR (*95% CI*)	Adjusted HR* (*95% CI*)
Continuous variable (per 100 μg/d)	762	494	1.06 (1.02–1.11)	1.04 (0.99–1.09)
Categorical variable				
Nonusers	752	479	Referent	Referent
< 1,200 μg/d	11	12	1.99 (1.02–3.88)	1.25 (0.63–2.47)
⩾ 1,200 μg/d	0.15	3	6.38 (1.57–25.19)	4.67 (1.06–20.53)

For definition of abbreviations, *see* Table 4.

* Adjusted for age, smoking status and smoking intensity, history of malignancy other than skin cancer, Seattle Index of Comorbidity score, and bronchodilator use.

68), and reduce airway inflammation (69). ICS have also been demonstrated to modulate production of prostaglandin E2 along the COX-2 inflammatory pathway (70), and have been demonstrated to suppress protooncogenes in human smokers (71). In addition, it is hypothesized that factors associated with decreased lung cancer risk, including dietary intake of phytoestrogens or reducing (and ideally complete cessation of) exposure to chronic tobacco smoke, may reduce oxidant injury and inflammation (4, 19, 20). Moreover, ICS may be chemopreventive in murine models (30). In brief, there is a growing abundance of literature that supports the role of inflammation in both mouse and human models of lung cancer. In mouse models, adrenalectomies have been demonstrated to enhance lung tumor formation (72), whereas there have been a number of studies that demonstrate that corticosteroids decrease the formation of lung cancer neogenesis. In models of chemically induced lung tumorgenesis, budesonide markedly decreased tumor formation potentially by modifying gene expression involved with cell cycle, signal transduction, and apoptosis (30, 73, 74). The effects of corticosteroids on inflammation and immunosuppression have been suggested. Potential mechanisms that have been implicated in lung cancer pathogenesis include a range of effects such as tightening of endothelial cell junctions, suppressing cytokine production, and effecting macrophage function through transcription factors (e.g., nuclear factor-κB), and by interfering with inducible nitric oxide synthase transcription and production (65). We hypothesize that higher doses of ICS reduce local airway inflammation, cell turnover, and propagation of genetic errors, and this may lead to subsequent reduction in lung cancer risk.

There are potential alternate explanations for our findings. First, patients with asthma may have been misclassified as having COPD. Because patients with asthma may not have had similar degrees of tobacco exposure, this would bias the finding in the direction of the described effects. We addressed this concern not only by adjusting for tobacco exposure but also by performing a series of analyses that restricted the cohort definitions to greater specificity for COPD and found that the cohort definitions had small effects on the point estimates. In addition, we performed stratified analyses demonstrating the effect was largely unchanged when the analyses were restricted to current and former smokers. In addition, recent reports suggest an increased risk of lung cancer associated with asthma in two well-described population-based cohort studies (75, 76). Second, the association may also have been spurious because of confounding by indication for ICS. However, we would expect that the confounding by severity of lung disease or symptoms of lung cancer would bias us in the opposite direction of the findings. Other markers of severity of lung disease, such as bronchodilator use, were associated with an increased risk of lung cancer, which would be consistent with bias by severity of COPD. In addition, among patients with previously diagnosed lung cancer, we found a strong association in the opposite direction of our primary finding, supporting our contention that the described association cannot be explained solely by confounding by indication for lung cancer symptoms. Third, it is possible that ICS may have decreased symptoms or exacerbations of COPD and led to a delay in detecting nodules or masses that had may have been otherwise identified had ICS not been prescribed. Finally, health behavior is strongly correlated with medication prescriptions, adherence, and health outcomes. However, predictors of health behavior, such as tobacco consumption, did not appear to influence our conclusions. Also, the protective effect of ICS persisted when we restricted the analyses only to those subjects who were adherent to ICS, suggesting that patient health behavior associated with medication adherence or a reduction in inhaled steroid use because of the symptoms or diagnosis of lung cancer does not account for our findings.

This study had several strengths. First, we studied patients from multiple centers, which minimized the chance that the patterns of diagnosis or treatment by any single physician or group of clinicians exerted undue influence on our results. Second, the cohort was drawn from a complete primary care clinic population, reducing the likelihood of selection biases, such as are often found in randomized trials. Third, we used a complete pharmacy database to ascertain inhaled corticosteroid exposure in a comparable, unbiased fashion. The VA provides medications free of charge or with minimal copayments; therefore, 98 to 99% of veterans enrolled in primary clinics obtain all prescription medications from VA pharmacies (33, 77).

Despite its strengths, this study also had some important limitations. First, exposure was assessed solely by refills recorded in the VA pharmacy database, not by whether the subjects actually used their medication after receipt. To address this issue, we required that patients be at least 80% adherent in filling their prescriptions. Nonetheless, this remains a limitation. Second, we were unable to confirm COPD diagnoses by spirometry. Agreement between medical chart review and ICD-9 diagnosis for COPD has been reported at 94.2% (78). In addition, we controlled for important factors associated with both prescriptions of ICS and lung cancer risk, including smoking status and intensity and inhaled bronchodilator use. Nonetheless, our inability to control for degree of airflow obstruction is an important limitation. Third, because there are relatively few women in our cohort, these results may not be generalizable to women with COPD. Finally, we cannot address whether the use of ICS reduced the risk of any particular cell type or was associated with the stage of cancer at presentation.

Lung cancer is the leading cause of cancer death among patients with and without COPD. Screening of high-risk groups is not currently recommended, and lung cancer is often found only after symptoms occur and, as a result, detected at advanced stages where the role of curative therapy is limited. Recent studies have shed important light on the potential role that chronic inflammation may play in the development of malignancies. We found that the direct delivery of inflammatory agents to the lung was associated with a decreased risk of developing lung cancer among patients at high risk. Although there is biologic plausibility to our findings, this observational study cannot conclude that ICS reduce lung cancer risk. Nonetheless, because the predominant biases are in the opposite direction of our findings, our results are suggestive and warrant additional studies to determine if they can be replicated.

Conflict of Interest Statement: T.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.W.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.L.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.B.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.M.U. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.H.A. owns 100 shares of Pfizer stock and received $1,500 for a GlaxoSmithKline-sponsored advisory roundtable.

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