Inhaled corticosteroids and the risk of lung cancer in COPD: a population-based cohort study

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ABSTRACT Inhaled corticosteroids (ICSs) are often prescribed in patients with chronic obstructive pulmonary disease (COPD). Their impact on the risk of lung cancer, a leading cause of mortality in COPD patients, remains uncertain.

Population-based linked administrative data between the years 1997 and 2007 from the province of British Columbia, Canada, were used to evaluate the association between lung cancer risk and ICS use in COPD patients. COPD was defined on the basis of receipt of three COPD-related prescriptions in subjects ⩾50 years of age. Exposure to ICS was incorporated into multivariable Cox regression models using several time-dependent methods ("ever" exposure, cumulative duration of use, cumulative dose, weighted cumulative duration of use and weighted cumulative dose).

There were 39 676 patients who met the inclusion criteria. The mean±SD age of the cohort was 70.7±11.1 years and 53% were female. There were 994 (2.5%) cases of lung cancer during follow-up. In the reference case analysis (time-dependent "ever" exposure), ICS exposure was associated with a 30% reduced risk of lung cancer (HR 0.70 (95% CI 0.61–0.80)). ICS exposure was associated with a decrease in the risk of lung cancer diagnosis over all five methods of quantifying exposure.

This population-based study suggests that ICS use reduces the risk of lung cancer in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterised by airflow limitation [1] and is one of the leading causes of death worldwide [2], with projections indicating that these numbers will rise in the next decade [3]. In mild-to-moderate COPD, lung cancer is a leading cause of mortality [4]. While smoking is a shared risk factor for COPD and lung cancer, evidence suggests that patients with COPD are at an increased risk of lung cancer, independent of cigarette smoking [5, 6].

Inhaled corticosteroids (ICSs) are commonly used for patients with COPD. While ICSs may not modify overall mortality in patients with moderate-to-severe COPD [7], ICSs improve quality of life [8, 9] and reduce the rate of acute exacerbations [10]. On the negative side, ICS use may increase the risk of pneumonia, especially among those with severe airflow limitation [11–13]. ICSs are nonspecific anti-inflammatory agents and, as such, they reduce inflammation in the airway of COPD patients [14]. Since persistent low-grade inflammation is thought to be an important contributor to lung cancer, long-term ICS use may have salutary effects in reducing the risk of lung cancer in COPD patients [15].

The primary objective of this study was therefore to evaluate the association between ICS use and the risk of lung cancer, using several definitions of medication exposure, in a population-based cohort of COPD patients.

Methods

Study population

This study used population-based linked administrative data for the province of British Columbia, Canada, to identify a cohort of COPD patients based on patients' filled prescriptions linked to a registry of cancer patients. The following linked databases were used: the Medical Services Plan data file provided physician billings for every encounter, under the universal provincial health insurance scheme [16], the Discharge Abstract Database, which includes hospital separations [17], the PharmaNet data file, which includes all prescriptions dispensed in British Columbia over the study period [18], and the British Columbia Cancer Registry (BCCR) file, which provides data on lung cancer diagnosis (the primary outcome), the diagnosis date, death due to cancer and cancer histology [19].

The cohort included individuals ⩾50 years of age who had filled at least three prescriptions for an inhaled anticholinergic medication or a short-acting β-agonist (SABA) in a 1-year rolling time window. The date of the first of these prescriptions was filled was considered to be the individual's index date (*i.e.* COPD "diagnosis"). A "wash-in" period was imposed to identify incident COPD patients. Each patient was required to have a 1-year period prior to their index date with no dispensed SABA or inhaled anticholinergic medication.

Latency period

To provide sufficient time for the use of ICS to affect the pathogenesis of lung cancer, a 1-year latency period was applied in the primary analysis, *i.e.* any medication exposure in the 1-year period prior to lung cancer, death or censoring was not counted as the pathogenesis of lung cancer was assumed to have already begun within 1 year prior to diagnosis (figure 1). Individuals with a total follow-up time <1 year were therefore excluded from the analyses.

ICS exposure

ICS users were initially identified according to the American Hospital Formulary Service (www.ahfsdruginformation.com) codes 520808, 680400 and 840600. Identified prescriptions meeting this criterion were scrutinised to ensure that only inhaled medications were considered.

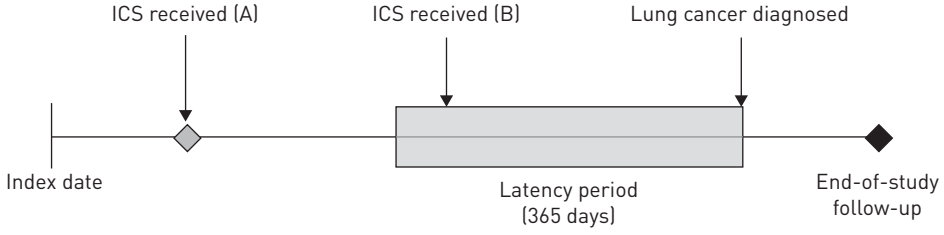

FIGURE 1 The latency period associated with medication exposure and lung cancer diagnosis. The application of the latency period (365 days) means that prescriptions received during the latency period (B), prior to the diagnosis of lung cancer in this illustration, are not counted as exposures. Prescriptions received after the index date and prior to the latency period (A) are counted as inhaled corticosteroid (ICS) exposures.

ICS exposure was quantified and incorporated into the multivariable regression models using several approaches that attempted to capture the nuances of inhaled medication exposure, particularly over longer follow-up periods. The time-dependent "ever" exposure was the primary exposure definition in this study. For this definition, a patient was considered exposed to an ICS at a given time during their follow-up, based on having filled a prescription after the start of follow-up and prior to the latency period. Cumulative duration of use was calculated by aggregating the length of time for which a patient had taken the medication. For this approach, the "days supply" of each dispensed prescription were aggregated for any given point during the study follow-up period. Cumulative dose was calculated by aggregating the total dose of medication prescribed to a specific patient follow-up. Each ICS prescription was converted to fluticasone-equivalent dosages to allow for comparison across different types of ICS. The recency-weighted cumulative duration of use approach was used to account for the duration of medication use while also accounting for when, in relation to the event, use occurred [20]. Prescriptions that occurred closer to the date of the event, or at the end of follow-up, were weighted higher than those that were received earlier in the study period. The assumption behind this method is that prescriptions dispensed more proximal to the outcome are likely to have a greater effect on the outcome than those prescriptions that were dispensed earlier in the follow-up period [20]. Similarly, the recency-weighted cumulative dose approach was used to simultaneously account for cumulative dose and the "recency" of the dispensation relative to the end of follow-up [20]. This method assumed that more recent doses of medication would have a greater impact on the study outcome.

Adjustment for potential confounders

Covariates thought to be potential confounders of the association between ICS exposure and lung cancer diagnosis were incorporated into a multivariable model. These covariates were assessed in the 1-year period prior to the latency period. The demographic covariates included: age, sex, neighbourhood income quintile-based residence and British Columbia health authority (regional health service) in which the patient resided. In addition, for each patient, the number of prescriptions filled, the number of hospital encounters, the number of inpatient hospital stays and the number of physician encounters were calculated. Finally, the Charlson Comorbidity Index was calculated based on health services use and considered as a potential confounding variable [21, 22].

Statistical analysis

A Cox regression model was used to estimate the hazard ratio associated with lung cancer diagnosis based on exposure to ICS, using the aforementioned exposure definitions, and adjusted for potential confounding variables [23, 24]. The primary analysis calculated the time from COPD diagnosis (the index date) to lung cancer diagnosis, death or end of study follow-up, whichever occurred first. Each potential confounder was added to the multivariable model *via* stepwise selection comparing Akaike Information Criterion (AIC) values [25]. Lower AIC values represent a better model fit than higher AIC values.

Hazard ratios and 95% confidence intervals are reported for each exposure metric as bivariate analyses and the adjusted multivariable analyses. AIC values are also presented to show the fit of each exposure metric. Statistical significance was achieved for p-values less than an α of 0.05.

Subgroup analysis: lung cancer histology

The BCCR file provided information on the histology of each lung cancer case. Using this data, we classified lung cancer into nonsmall cell lung cancer (NSCLC), small cell lung cancer (SCLC) or other carcinomas. Using the same analytical approach, multivariable models were fitted with the outcome variables SCLC and NSCLC.

Sensitivity analyses

Several sensitivity analyses were conducted based on our assumption of the latency period. Thus, in sensitivity analyses, the latency period was removed altogether (*i.e.* 0 days), reduced to 180 days and extended to 2 years, to explore whether study results were robust to this assumption. In addition, because lung cancer incidence is quite low in those <65 years of age [26, 27], in another sensitivity analysis the cohort age restriction was increased from ⩾50 to ⩾65 years.

An additional sensitivity analysis was conducted to account for the fact that the risk of death would be a competing risk with the primary outcome. This concern was addressed using two sensitivity analyses. First, lung cancer and death were treated together as a composite outcome in the multivariable analysis. Second, a competing risks analysis was conducted (reported in supplementary table S1).

Finally, to ensure that our results were robust to different definitions of the COPD cohort, two additional analyses were conducted with more specific alternative cohort definitions of COPD. In the first, the cohort

was restricted to only those who received an inhaled anticholinergic medication. This results in a very specific case definition as anticholinergics in this patient population can only be prescribed after objective diagnosis of COPD through spirometry. For the second alternative definition, we excluded any patient that had a physician encounter or an inpatient/outpatient hospitalisation for asthma (International Classification of Diseases, Ninth Revision code 493) (reported in supplementary table S2).

Results

A cohort of 39 676 patients was identified that met the primary inclusion criteria. The mean±SD age of the patients on the index date was 70.7±11.1 years and 53.4% were female. The mean±SD follow-up time was 5.2±2.3 years (tables 1 and 2).

ICS use

There were 372 075 dispensed prescriptions for ICS within the cohort and 28 314 (71.2%) distinct users of ICS. Most patients filled more than one prescription for ICS, with a median (interquartile range (IQR)) of 8 (3–19) prescriptions filled per patient during the follow-up period. The most frequently prescribed ICS was fluticasone propionate and the median (IQR) daily dose was 0.64 (0.5–1.2) mg. The median (IQR) days of ICS supplied for each individual per (filled) prescription was 60 (30–90) days. Bivariate regression results for ICS exposure are reported in table 3.

Lung cancer diagnoses

Initially, 1966 cases of lung cancer were identified within the cohort during the follow-up period. Lung cancers that were diagnosed within 1 year of the index date were removed, which resulted in 994 cases of

TABLE 1 Demographics of the chronic obstructive pulmonary disease (COPD) cohort

Subjects	39 676
Age years	70.7±11.1
Age distribution years	
50– <60	8241 (21.0)
60– <70	10 210 (25.7)
70– <80	12 439 (31.4)
⩾80	8786 (22.1)
Female	21 189 (53.4)
Income quintile	
1 (lowest)	9681 (26.6)
2	7841 (21.6)
3	6828 (18.8)
4	6360 (17.5)
5 (highest)	5679 (15.6)
British Columbia health authority	
Interior	8569 (22.8)
Fraser	11 354 (30.2)
Vancouver Coastal	7740 (20.6)
Vancouver Island	7522 (20.0)
Northern	2465 (6.6)
Hospitalisations	
Any reason	6624 (16.7)
COPD-related	1083 (2.7)
CVD-related	512 (1.3)
Physician encounters (any reason)	11 (3–22)
CCI category[#]	
0	31 354 (79.0)
1	6303 (15.9)
2	1176 (3.0)
3	843 (2.1)
Combination therapy	6585 (16.5)
Prescriptions filled (any reason)	21 (7–44)

Data are presented as n, mean±SD, n (%) or median (interquartile range); where percentages do not add to 100% the reason is due to rounding. CVD: cardiovascular disease; CCI: Charlson Comorbidity Index. [#]: category 0 is a CCI score of 0, category 1 is a CCI score of >0–2, category 2 is a CCI score of >2–3 and category 3 is a CCI score of >3.

TABLE 2 Bivariate regression results for covariates considered for inclusion in the multivariable model, with time to lung cancer diagnosis as the outcome

	Hazard ratio (95% CI)	p-value
Age	1.01 (1.00–1.01)	0.001
Age category years		
<60	Reference	
60– <70	2.02 (1.67–2.43)	<0.001
70– <80	2.33 (1.95–2.80)	<0.001
⩾80	1.29 (1.03–1.61)	0.241
Male	1.39 (1.24–1.56)	<0.001
British Columbia health authority		
Interior	1.29 (0.98–1.71)	0.074
Fraser	1.23 (0.93–1.62)	0.148
Vancouver Coastal	1.04 (0.78–1.40)	0.769
Vancouver Island	1.46 (1.10–1.94)	0.008
Northern	Reference	
Income quintile		
5	Reference	
4	1.27 (1.03–1.57)	0.025
3	1.14 (0.92–1.41)	0.215
2	1.23 (1.00–1.50)	0.049
1	1.24 (1.02–1.51)	0.030
Total number of prescriptions	1.00 (0.99–1.00)	<0.001
CCI score (continuous)	1.06 (0.97–1.16)	0.1853
CCI score (categorical)		
0	Reference	
1	1.15 (0.98–1.36)	0.093
2	0.94 (0.62–1.40)	0.746
⩾3	0.90 (0.55–1.48)	0.681
Inpatient stay	3.57 (3.16–4.03)	<0.001
Number of hospitalisations	1.66 (1.64–1.68)	<0.001
COPD-related hospitalisation	2.56 (2.00–3.27)	<0.001
CVD-related hospitalisation	1.04 (0.58–1.88)	0.896
Combination therapy (ICS/LABA)	1.27 (1.11–1.47)	0.007
Number of physician encounters	1.02 (1.02–1.02)	<0.001
Oral glucocorticoid use	1.09 (0.91–1.30)	0.340

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; ICS: inhaled corticosteroid; LABA: long-acting β-agonist.

lung cancer. The median (IQR) age at lung cancer diagnosis was 71.3 (65.6–76.4) years, 46.2% of lung cancers occurred in females and 854 (85.9%) were classified as NSCLC on histology.

Multivariable analysis

Although the magnitude of the association varied according to the specific exposure metric employed, the direction of the association was consistent across all multivariable analyses. In the reference case, which

TABLE 3 Association between inhaled corticosteroid (ICS) use and lung cancer, using five different definitions of exposure, adjusted for age and sex only

Exposure metrics	Bivariate hazard ratio (95% CI)	Age- and sex-adjusted hazard ratio (95% CI)
Time-dependent ICS exposure	0.70 (0.61–0.80)	0.72 (0.63–0.83)
Cumulative duration[#]	0.89 (0.84–0.95)	0.90 (0.84–0.96)
Cumulative dose[#]	0.79 (0.66–0.95)	0.80 (0.67–0.95)
Recency-weighted duration of use	0.75 (0.68–0.82)	0.76 (0.68–0.83)
Recency-weighted cumulative dose	0.62 (0.48–0.80)	0.62 (0.49–0.80)

[#]: measured as a continuous variable.

TABLE 4 Fully adjusted analysis of the association between inhaled corticosteroid (ICS) use and lung cancer, applying five different exposure definitions with Akaike Information Criterion (AIC) values: multivariable regression[#]

Exposure metrics	Hazard ratio (95% CI)	p-value	AIC
Time-dependent ICS exposure	0.70 (0.61–0.80)	<0.001	19 132
Cumulative years of use[¶]	0.89 (0.83–0.95)	<0.001	19 141
Cumulative dose[¶]	0.83 (0.72–0.97)	0.0201	19 149
Recency-weighted duration of use	0.74 (0.66–0.82)	<0.001	19 116
Recency-weighted cumulative dose	0.57 (0.43–0.74)	<0.001	19 133

[#]: multivariable regression analysis was adjusted for the following covariates: age, sex, region, income quintile, inpatient hospitalisation, number of physician encounters, chronic obstructive pulmonary disease hospitalisation, year of cohort entry, Charlson Comorbidity Index score, total number of prescriptions received, oral glucocorticoid use and time-dependent statin exposure; [¶]: measured as a continuous variable.

classified ICS exposure as a time-dependent variable, the adjusted HR was 0.70 (95% CI 0.61–0.80), indicating a 30% reduction in lung cancer risk associated with the use of ICS. Exposure to ICS, as measured by the two recency-weighted metrics, showed similar results. The recency-weighted duration of use exposure metric showed ∼26% reduction in lung cancer risk (HR 0.74 (95% CI 0.66–0.82) per weighted year) and the use of a recency-weighted cumulative dose metric resulted in an HR of 0.57 (95% CI 0.43–0.74), *i.e.* a 43% reduction in the risk of lung cancer per gram of ICS use. For each multivariable analysis using distinct exposure metrics, AIC values were compared to assess the best model fit. Of the exposure metrics presented in table 4, the best (lowest) AIC value was the model that used the recency-weighted duration approach.

Lung cancer histology

The analyses of specific lung cancer histology also suggested a protective effect of ICS (table 5). In multivariable analysis, the use of ICS (reference case definition) was associated with a 30% reduction in the risk of NSCLC (HR 0.70 (95% CI 0.60–0.82)). For SCLC, use of ICS was also associated with a risk reduction, although there was more uncertainty around the point estimate (HR 0.59 (95% CI 0.40–0.87)), likely due to the small number of SCLC cases (n=117).

Sensitivity analyses

When the latency period was removed altogether, using the time-dependent exposure metric, the multivariable hazard ratio was statistically significant and in the opposite direction (HR 1.12 (95% CI 1.02–1.40)). Using a 180-day latency period, the estimated hazard ratios for ICS use were in the expected direction, indicating a protective effect of ICS use for lung cancer risk, but the results were not statistically significant. Extending the latency period to 2 years resulted in ICS use being associated with a substantial risk reduction for lung cancer. To address concerns over death being a competing risk for lung cancer, a sensitivity analysis using a competing risk model produced results consistent with those of the primary

TABLE 5 Subgroup analyses based on lung cancer histology: multivariable regression analysis with time to nonsmall cell lung cancer (NSCLC) or small cell lung cancer (SCLC) diagnosis as the outcome variables

	Hazard ratio (95% CI)	p-value
NSCLC		
Time-dependent ICS exposure[#]	0.70 (0.60–0.82)	<0.001
Recency-weighted duration of use[¶]	0.76 (0.68–0.84)	<0.001
SCLC		
Time-dependent ICS exposure	0.59 (0.40–0.87)	0.008
Recency-weighted duration of use	0.56 (0.39–0.80)	0.002

ICS: inhaled corticosteroid. [#]: reference case for the analysis; [¶]: the recency-weighted duration of use exposure metric is presented because it was selected as the best model based on Akaike Information Criterion values (an *a priori* criterion).

analysis (supplementary table S1). Finally, the results of the analysis using alternative cohort definitions both showed a statistically significant protective effect from use of ICS, consistent with our primary results (supplementary table S2).

Discussion

This study evaluated the relationship between exposure to ICS and lung cancer risk using a population-based cohort of COPD patients and showed that ICS, using an array of exposure definitions and adjusted for a range of potential confounders, was associated with a reduced risk of lung cancer. In the reference case analysis, ICS use was associated with a 30% decrease in the risk of lung cancer. Moreover, the results of our analysis suggest that the recency-weighted duration of use approach, a method that accounts for the duration of use of ICS while simultaneously accounting for the timing of the exposure relative to the lung cancer diagnosis, was the best method for measuring this association and resulted in a >25% risk reduction for lung cancer.

There has been no clinical trial that has specifically addressed this research question [28]. Previously published observational data suggested a protective effect of ICS on the risk of lung cancer [29, 30]; however, these studies had significant limitations, such as patient populations that were not representative of the COPD population and a lack of information on the histological subtypes of lung cancer. A recent study by Sørli *et al.* [31] found no significant protective effect of ICS use on lung cancer risk; however, this study also had several limitations. For example, ICS exposure was based on self-report and not based on objective administrative or health records. Moreover, because of how ICS exposure was recorded, the authors could not account for the time dependency of medication exposure in their analysis.

Implementation of a latency period in the primary analysis is a valuable contribution of this study to the literature. Lung cancer is often diagnosed at an advanced stage and is likely to have been present for a considerable period prior to the clinical diagnosis. Consistent with this notion, we found that the removal of the latency period altogether resulted in an increase in the risk of lung cancer with ICS use (table 6). Given what is known about the pathogenesis of lung cancer, this is likely an illustration of protopathic bias [32]. In view of the biology of tumour growth in lung cancer, the assumption of a 1-year latency period seems appropriate [33], but this may require further research.

While the mechanism by which COPD is associated with an increased risk of lung cancer is not well established, there is evidence to suggest that inflammation may be an important contributing factor in the causal pathway. Thomsen *et al.* [34] evaluated the association between levels of systemic inflammation using multiple biomarkers (C-reactive protein, fibrinogen and leukocyte count) and the risk of lung cancer in COPD patients. The authors found a statistically significant increased risk of lung cancer when two of these three levels were elevated (HR 2.14 (95% CI 1.21–3.77)), while controlling for smoking status, which

TABLE 6 Sensitivity analyses of different lengths of the latency period: multivariable regression

	Hazard ratio (95% CI)	p-value
Latency period		
None		
Time-dependent ICS exposure[#]	1.20 (1.02–1.40)	0.024
Recency-weighted duration of use[¶]	1.19 (1.11–1.28)	<0.001
6 months		
Time-dependent ICS exposure	0.91 (0.78–1.05)	0.197
Recency-weighted duration of use	0.97 (0.89–1.05)	0.476
1 year[+]		
Time-dependent ICS exposure	0.70 (0.61–0.80)	<0.001
Recency-weighted duration of use	0.74 (0.66–0.82)	<0.001
2 years		
Time-dependent ICS exposure	0.32 (0.28–0.37)	<0.001
Recency-weighted duration of use	0.31 (0.26–0.37)	<0.001
Cohort (age ⩾65 years)		
Time-dependent ICS exposure	0.66 (0.56–0.77)	<0.001
Recency-weighted duration of use	0.70 (0.62–0.79)	<0.001

ICS: inhaled corticosteroid. [#]: reference case for the analysis; [¶]: the recency-weighted duration of use exposure metric is presented because it was selected as the best model based on Akaike Information Criterion values (an *a priori* specified criterion); [+]: a 1-year latency period was assumed in the primary analysis and is presented here for comparison.

increased to four times greater risk (HR 4.00 (95% CI 2.12–7.54)) if all three levels were elevated compared with those with no elevated levels. Overall, these data suggest that inflammation is an important consideration in COPD and could be considered when treating patients. Further research into prediction rules to identify individuals at high risk of lung cancer, particularly in a screening context, would also be helpful in treating these patients [35, 36].

The recency-weighted approaches are intuitively attractive as they simultaneously accounted for the duration of use, the dosage and the time during follow-up when the prescription was filled. This method has been used in previous studies [37, 38], but primarily in the context of acute medical events, never for a disease such as lung cancer characterised by induction and latency periods. Both methods of recency-weighting exposure resulted in hazard ratios that indicated a reduction in lung cancer risk and the corresponding AIC value for recency-weighted duration of use model was superior to the other approaches of defining medication exposure.

This study also has limitations which require acknowledgement. First, while administrative data are a valuable source of information, they are limited in the scope of variables that could inform exposure–outcome associations. For example, while filled prescriptions are recorded, there is no data on whether patients actually use their medication. Second, no clinical data were available for these patients and the classification of patients as having COPD is based solely on their prescription profiles. However, a similar definition used to identify these COPD patients has been utilised previously [39, 40] and is likely a sensitive rather than specific definition. Another possibility is that some patients in the cohort may have had asthma. Recent evidence also supports a reduced risk of lung cancer associated with ICS use in patients with asthma [41]. Importantly, the objective of our study was to determine whether ICS may offer a protective effect for lung cancer risk in those with an elevated risk of lung cancer, regardless of whether the patient has diagnosed COPD or asthma–COPD overlap. Third, this study is subject to the limitations common to most observational studies, where unmeasured confounding may be present. However, the population-based nature of the data, the systematic approach to inclusion of potential confounders and the use of a broad set of exposure metrics should have minimised the potential for bias. Moreover, the magnitude of the association between ICS exposure and lung cancer risk, and the consistency of this association across all of the exposure metrics, enhances the validity of our results. Lastly, no data on patients' smoking status were available for this analysis. While an obvious limitation, given the literature on COPD, it can be reasonably assumed that the majority of these patients do have a history of smoking or may indeed be current smokers. If the use of ICS were differential between smokers and nonsmokers, then current smokers or those with a history of smoking are likely to be at higher risk of lung cancer. These patients are also likely to have more severe disease and, similarly, more likely to be prescribed ICS, which might result in a conservative bias of the estimated effects.

The appropriate use of ICS in COPD patients is often debated and not all patients might benefit from the use of ICS. The clinical benefits and risk of use in an individual patient must be weighed by the physician. This study, however, indicates that potential benefits may accrue from ICS use in COPD patients in terms of reduced lung cancer risk and that sustained use may be associated with reduced risk of lung cancer. These results highlight the importance of properly identifying which patients might be at the highest risk of lung cancer, to enhance the therapeutic benefits of ICS in these COPD patients.

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