Early View

Original article

Inhaled corticosteroid use and the incidence of lung cancer in COPD

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Running title: Inhaled corticosteroids and lung cancer in COPD

Take home: Large cohort study finds no reduction in lung cancer incidence with inhaled corticosteroids in COPD. Other observational studies reporting significant reductions likely affected by time-related biases and confounding from the inclusion of asthma patients

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ABSTRACT

Background: Inhaled corticosteroids (ICS) are suggested as potential chemoprevention of lung cancer. Several observational studies in patients with COPD reported inconsistent results, either significant reductions in lung cancer incidence with ICS use or no effect. We assessed this association, using an approach that avoided biases affecting some of the studies.

Methods: A cohort of patients with COPD, new users of long-acting bronchodilators over 2000-2014, was formed using the Quebec healthcare databases, and followed until 2015 for a first diagnosis of lung cancer. A one-year delay after cohort entry was used to avoid protopathic bias and a one-year latency period was included after the initiation of ICS use. A time-dependent Cox regression model was used to estimate the hazard ratio (HR) of lung cancer associated with ICS exposure, adjusted for covariates.

Results: The cohort involved 58,177 subjects, including 63% receiving ICS, with 954 lung cancers occurring during a mean follow-up of 5 years. The adjusted HR of lung cancer associated with any ICS exposure was 0.94 (95% CI: 0.81-1.07), relative to no ICS use. The HR with longer (>4 years) time since ICS initiation was 0.86 (95% CI: 0.70-1.07), while with higher mean daily ICS dose (>1000 mcg fluticasone equivalents) was 1.50 (95% CI: 0.88-2.57).

Conclusions: Inhaled corticosteroid use is not associated with a reduction in lung cancer incidence in patients with COPD. Observational studies reporting such reduction may have been affected by time-related biases and the inclusion of patients with asthma. The proposition of a randomized trial warrants some caution.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now the third leading cause of death in the world and is linked to several comorbidities.[1-3] Lung cancer is one such comorbidity whose incidence is significantly higher in patients with COPD than in the general population.[4] Several factors have been associated with variations in the incidence of lung cancer in patients with COPD.[5]

In linking the two diseases, the inflammation associated with lung cancer and its potential reduction with long-term inhaled corticosteroid (ICS) use has been examined. Some observational studies reported that ICS use is associated with a lower incidence of lung cancer.[6,7] Certain studies also suggest that this reduction may be dose-dependent.[8-11] Other observational studies, however, did not find an association between ICS use and lung cancer incidence.[12-14] In addition, data from large randomized trials of ICS in COPD found no decreased incidence of lung cancer.[15] Nevertheless, some find the evidence sufficiently compelling to suggest the conduct of a prospective randomized controlled trial.[16] This issue has important implications as ICS are now used extensively in the treatment of COPD, although the appropriateness of such widespread use has been questioned.[17]

These discrepancies among observational studies, as well as with randomized trial data, could be due to the introduction of bias, including time-related biases leading to exposure and outcome misclassification. In this paper, we use data from the Canadian Province of Quebec to assess the association between ICS use and lung cancer incidence, using a study design and data analysis techniques that avoid these sources of bias.

METHODS

Sources of data

The study was conducted using databases from the *Régie de l'Assurance Maladie du Québec* (RAMQ), the administration that manages the universal health insurance plan for the eight million residents of the province of Québec. In particular, these comprise information from all hospital discharge summaries in the Province, including information on cancer diagnoses, for which the sensitivity was shown to be high for lung cancer.[18] They also include data on medical services rendered and prescription drugs dispensed to all people aged 65 years or older, welfare recipients and, since 1996, other residents who opt to join the provincial drug plan. These databases have been used previously to study the epidemiology of COPD and the effects of its treatments.[19-22]

Cohort definition

The study cohort was formed by first identifying all subjects with three or more prescriptions for long-acting muscarinic antagonists (LAMA) or long-acting ß-agonists (LABA, not combined with ICS), dispensed in any one-year period and on at least two different dates, between 2000 and 2014. To ensure a new-user cohort of COPD treated patients, we included only subjects who had no prescription for these drugs in the one-year period prior to cohort entry, defined by the first of the three prescriptions, necessitating one-year enrollment prior to cohort entry. Subjects had to be at least 50 years old at cohort entry. All subjects were followed from cohort entry until the first lung cancer diagnosis, death or the end of insurance drug coverage or data availability (31 December 2015). Patients with a diagnosis of lung cancer or a prescription for an ICS in the year prior to cohort entry were excluded.

Outcome classification

The first lung cancer event occurring during follow-up was identified from inpatient and outpatient diagnoses (ICD-9 162.X, ICD-10 C33-C34). Protopathic bias is plausible in this context since early respiratory symptoms of a yet undiagnosed lung cancer can be treated with bronchodilators, so that some new users of a LABA or LAMA may have initiated their treatment for an imminent lung cancer.[23] Thus, all subjects with less than one year of follow-up, including those with a lung cancer diagnosis in the first year of follow-up after cohort entry, were excluded.

Exposure classification

All outpatient prescriptions for ICS, including beclomethasone, budesonide, triamcinolone, fluticasone, mometasone, ciclesonide and flunisolide, alone or in a combination inhaler, dispensed after cohort entry were identified. The dose of ICS of each prescription was converted to fluticasone equivalents.[24]

To avoid immortal time bias, subjects were classified as unexposed to ICS prior to their first prescription for ICS and exposed subsequently.[25] Moreover, to include a biologically plausible period of the effect of ICS on lung cancer incidence, we defined a one-year latency period after the date of the first ICS prescription.[26] Thus, all person-time in this latency period was also classified as unexposed to ICS, while only the person-time after this one-year latency period was classified as exposed. Consequently, lung cancer events

occurring during this one-year latency period were classified as unexposed, and only those occurring subsequently were classified as exposed to ICS.

Data analysis

We estimated the crude rates and rate ratios of lung cancer incidence associated with ICS exposure according to the person-time under exposure. We used time-dependent Cox proportional hazards regression models to estimate the hazard ratio of lung cancer incidence associated with ICS exposure according to the time-dependent change in ICS exposure during follow-up, adjusted for potential confounders measured at cohort entry. These covariates included age, sex, COPD hospitalization and exacerbation in the year prior to cohort entry, as well as comorbidity at cohort entry, including cardiovascular and cerebrovascular diseases, diabetes, renal disease, other cancers (not lung), dementia, and rheumatoid disease, among others.

To assess the effect of treated time on lung cancer incidence, the time since the first ICS prescription was categorized as <2, 2-4 and >4 years. To assess the effect of ICS dose, the time-dependent mean daily dose was computed by summing the fluticasone dose-equivalents of all ICS prescriptions dispensed from the first prescription to the time point of the risk set defined by the Cox hazards model, divided by the time from first ICS prescription to the risk set time. The mean ICS dose categorized as <500, 500-1000 and >1000 mcg of fluticasone equivalents. Cubic splines were also used with the Cox proportional hazards regression model to estimate the hazard ratio of lung cancer incidence over time since ICS initiation and by the mean ICS daily dose.

We performed sensitivity analyses to assess the impact of the various time-related biases observed in some of the observational studies to date. Thus, we removed the one-year protopathic bias criterion, removed the one-year latency period, and introduced immortal time bias by classifying a patient who received ICS at any time as exposed to ICS as of cohort entry. All analyses were performed using SAS version 9.4. The study was approved by the Ethics Committee of the Jewish General Hospital (JGH Protocol #16-225), Montreal, Quebec, Canada.

RESULTS

The study cohort initially included 62,146 COPD patients who were new users of LABA or LAMA, 50 years of age or older, between 2000 and 2014 (Figure 1). The mean follow-up was 4.9 years (maximum 16 years), during which 1,518 were diagnosed with lung

cancer (incidence rate 4.98 per 1000 person-years). A total of 3,969 patients, including 564 lung cancers, who had less than one year of follow-up were excluded to avoid protopathic bias.

Thus, after considering the one-year protopathic period, the final study cohort included 58,177 COPD patients of mean age 71 years (SD 10) at cohort entry and 48% were female. There were 36,719 (63%) subjects who received a prescription for ICS at some point during follow-up. The mean time between cohort entry and the first ICS prescription among the users was 1.2 (range 0-15) years. Table 1 presents the subject characteristics of the study cohort at baseline, by use of ICS during follow-up. In the year prior to cohort entry, 5.4% had been hospitalized for COPD and 20% had a COPD exacerbation, defined by a prescription for an oral glucocorticoid or a hospitalisation for COPD.

The overall rate of lung cancer incidence in the final study cohort is 3.15 per 1000 person-years, including no events in the first year. After considering the one-year protopathic and one-year latency periods, the adjusted hazard ratio of lung cancer incidence with time-dependent ICS use is 0.94 (95% CI: 0.81-1.07) relative to non-use (Table 2). There is a trend towards a lower hazard ratio with longer time (>4 years) since first ICS prescription (hazard ratio 0.86; 95% CI: 0.70-1.07) relative to non-use (Table 2 and Figure 2). The effect fluctuates with respect to the mean daily ICS dose, as less than 500 mcg of fluticasone equivalents is associated with a lower incidence of lung cancer (hazard ratio 0.83; 95% CI: 0.71-0.96) while for 500-1000 mcg the hazard ratio is 1.29 (95% CI: 1.06-1.56) relative to non-use (Table 2 and Figure 3).

Table 3 presents the sensitivity analyses to assess the impact of protopathic, latency and immortal time biases. When immortal time was properly dealt with by classifying ICS exposure as time-dependent, the effects of ignoring the protopathic and latency periods were found to be minor, resulting in a hazard ratio of 1.08 (95% CI: 0.97-1.20), of similar magnitude to the hazard ratio of 0.94 (95% CI: 0.81-1.07) that accounted for both periods. On the other hand, the introduction of immortal time bias that misclassifies the immortal time prior to the first ICS prescription as exposed to ICS instead of unexposed resulted in significant underestimations of the hazard ratio, including an estimate of 0.48 (95% CI: 0.42-0.55) even after accounting for one-year protopathic and latency periods.

DISCUSSION

Using a large cohort of close to 60,000 new users of COPD medications followed for up to 16 years, we found that inhaled corticosteroid use is not associated with a reduction

in the incidence of lung cancer. In addition, there was no effect by duration of ICS use, but low doses of ICS were associated with a lower incidence of lung cancer and higher doses with a higher incidence.

The reduction in lung cancer incidence with ICS use was reported by several observational studies, with some suggesting that this reduction may be dose-dependent.[6-11]. However, other observational studies did not find an association.[12-14] Moreover, a review identified randomized trials of ICS in COPD that reported data on lung cancer.[15] None of the trials found a reduction in lung cancer incidence with ICS.[27-30]. Furthermore, the Salford COPD randomized trial reported 8 lung cancer related deaths in the fluticasone furoate-vilanterol arm compared with 2 in the usual care arm, though no data were reported on lung cancer incidence.[31]

An important methodological aspect that can explain the reduction in lung cancer incidence found in some of the observational studies is the confounding potential of the "asthma factor", which has affected several studies of ICS effectiveness in COPD.[32] Indeed, patients with asthma are more likely to receive ICS and less likely to develop lung cancer, partly by the differences in smoking prevalence. In some of the studies, a large proportion of the subjects also had a diagnosis of asthma, with minimal or no adjustment for asthma, nor stratification.[6,9,11] In one study, the included patients were 40 years of age or older with a COPD diagnosis or a "self-report chronic lung disease", but did not report on asthma.[8] Conversely, patients with emphysema who have a higher incidence of lung cancer may be less likely to be treated with ICS because of more severe dyspnea.[33] Thus, the inability to identify emphysema in the database can also result in a confounded reduction in lung cancer incidence with ICS. Thus, residual confounding by asthma prevalence, asthma severity, emphysema and smoking cannot be ruled out for the significant reductions in lung cancer incidence with ICS use reported in these studies.

Time-related biases are another important methodological issue affecting some of these studies. Our sensitivity analyses demonstrate that immortal time bias can have the greatest impact on these studies. Immortal time bias results from the exposure definition to ICS, for example "based on having filled a prescription after the start of follow-up", which will cause a patient to be classified as exposed to ICS during the entire follow-up, even during the follow-up time before their first ICS prescription.[7] The time between cohort entry and the first ICS prescription is called "immortal" and the misclassification of this immortal and unexposed period as "exposed" will result in immortal time bias.[34,35] Two of the studies that reported important reductions in lung cancer incidence with ICS used this

approach and were thus affected by immortal time bias.[7,10] One study that specifically avoided this bias by properly classifying exposure over time reported an elevated hazard ratio of lung cancer incidence with ICS (HR 2.23; 95% CI: 1.31-3.79).[13]

Few of the observational studies included a latency period in the analysis. This can be problematic since, without such latency consideration, a study will classify an incident lung cancer as exposed to ICS even if it was diagnosed a very short time after the first ICS prescription, which can bias the effect estimate.[26,36] Indeed, our sensitivity analyses showed that the hazard ratio estimate of 0.94 (95% CI: 0.81-1.07) was increased to 1.08 (95% CI: 0.97-1.20) and 1.19 (95% CI: 1.04-1.37) when the one-year latency period was not included. Finally, protopathic bias is likely in this context since early respiratory symptoms of a yet undiagnosed lung cancer can be treated with bronchodilators before the clinical diagnosis is posed.[23] However, few observational studies considered this source of bias. Our sensitivity analyses showed that this bias can affect the hazard ratio either way.

A strength of our observational study is the new-user design that identified new users of long-acting bronchodilators without ICS, which defines a clear cohort entry point. Moreover, our study was designed to specifically avoid several of the time-related biases affecting some of the previous studies, namely immortal time, latency time and protopathic biases. The use of the Cox proportional hazards model is also noteworthy as it takes into account changes in ICS use and lung cancer incidence over follow-up time. Indeed, using simple rates produced a crude RR of 1.37 versus the crude HR of 0.92 (Table 2). However, while the former assumes that the incidence rate of lung cancer is constant over follow-up time, the later allows for the lung cancer incidence to increase with time, adjusting for increasing ICS use over time.

Our study is first limited by exposure measures based on dispensed prescriptions, which could introduce some misclassification as it is unclear if the medication was used and the uncertainty as to proper inhaler technique in a real world setting. Also, the cohort may have included some patients with asthma.[37] However, this number is likely small because of the 50 years of age cut-off for treatment initiation and the cohort entry criterion based on initiating treatment exclusively with long-acting bronchodilators that do not include ICS, a treatment approach contraindicated for asthma. Nevertheless, residual confounding from unmeasured confounders cannot be ruled out, in particular the unavailability of smoking data along with the inclusion of some patients who develop asthma after age 50 and the lack of identification of patients with emphysema. These unmeasured confounders and residual confounding from COPD severity may explain our dose-response findings of low doses of

ICS associated with a lower incidence of lung cancer and higher doses with a higher incidence, although these could also be due to random fluctuation.

In view of the methodological limitations present in several observational studies and the absence of evidence from randomized safety trial data, it may be prudent to put some more thought into the proposition of a placebo-controlled randomized trial at this time.[16] Our observational study that accounted for the sources of bias present in other studies did not find an association between ICS use and lung cancer incidence. Several randomized trials have been conducted in COPD on the basis of observational studies, such as the studies reporting major reductions in all-cause mortality with ICS in COPD that were shown to be affected by immortal time bias.[32,38,39] These large beneficial effects could not be corroborated by the subsequent randomized trials.[27,40] Moreover, a trial of ICS to prevent lung cancer in COPD may also be practically unattainable as it would require a very large number of patients with COPD who do not use ICS. Indeed, over 30,000 patients with COPD would be needed for such a trial to confirm the findings of the observational study.

Overall, observational studies are certainly valuable to assess the effects of medications in the real world clinical setting and to complement or form the basis for randomized trials. Our study did not find that ICS use reduces the incidence of lung cancer in patients with COPD. It appears that the previous studies that showed such a reduction were affected by time-related and some confounding biases that our study design was intended to avoid. Thus, for the question of ICS potentially preventing lung cancer, the proposition of a placebo-controlled randomized trial is still premature and would warrant some caution.

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Table 1

Baseline characteristics of study cohort of patients with COPD initiating treatment with LABA or LAMA, Quebec, 2000-2014, according to use of ICS during follow-up

	No ICS	Any ICS
Number of patients	21,459	36,718
Female sex, n(%)	9551 (44.5)	18,392 (50.1)
Age, in years, mean (SD)	72.3 (10.2)	71.1 (9.8)
Age group, n (%)		
50-64 years	4923 (22.9)	9349 (25.5)
65-74 years	7115 (33.2)	13,240 (36.1)
75-84 years	6807 (31.7)	10,884 (29.6)
≥85 years	2614 (12.2)	3245 (8.8)
COPD events in year prior to cohort entry, n (%)		
Hospitalization	818 (3.8)	2304 (6.3)
Exacerbations		
None	18,348 (85.5)	28,438 (77.4)
1	2437 (11.4)	6520 (17.8)
2 or more	674 (3.1)	1760 (4.8)
Comorbidity in year prior to cohort entry, n (%)		
Myocardial infarction	1206 (5.6)	1828 (5.0)
Heart failure	2282 (10.6)	3355 (9.1)
Peripheral vascular disease	1721 (8.0)	2560 (7.0)
Cerebrovascular disease	964 (4.5)	1495 (4.1)
Diabetes	4994 (23.3)	7769 (21.2)
Renal disease	1730 (8.1)	2346 (6.4)
Cancer (not lung)	1247 (5.8)	1924 (5.2)
Metastatic cancer	434 (2.0)	605 (1.6)
Dementia	841 (3.9)	962 (2.6)
Rheumatoid disease	317 (1.5)	515 (1.4)
Peptic ulcer	173 (0.8)	320 (0.9)
Liver disease	515 (2.4)	731 (2.0)
Hemiplegia or paraplegia	179 (0.8)	303 (0.8)

Table 2

Crude and adjusted hazard ratios of lung cancer incidence with ICS use versus non-use in patients with COPD, by time since initiation and by mean daily dose

	Number with events	Person-years	Rate per 1000 per year	Crude HR	Adjusted* HR (95% CI)
Any ICS use					
None (reference)	447	166,296	2.7	1.00	1.00 (Reference)
Any ICS	507	136,293	3.7	0.92	0.94 (0.81-1.07)
Time since ICS initiation					
None (reference)	447	166,296	2.7	1.00	1.00 (Reference)
0-2 years	134	30,631	4.4	1.06	1.07 (0.88-1.31)
>2-4 years	156	45,867	3.4	0.86	0.87 (0.71-1.06)
>4 years	217	59,795	3.6	0.84	0.86 (0.70-1.07)
Mean daily dose† since ICS initiation, mcg					
None (reference)	447	166296	2.7	1.00	1.00 (Reference)
>0 to <500 mcg	343	105436	3.3	0.80	0.83 (0.71-0.96)
500 to <1,000 mcg	150	28534	5.3	1.29	1.29 (1.06-1.56)
≥1,000 mcg	14	2324	6.0	1.48	1.50 (0.88-2.57)

* After adjusting for covariates in Table 1.

† Dose across different ICS converted to fluticasone equivalents[24]

Table 3

Sensitivity analyses for the crude and adjusted hazard ratios of lung cancer incidence with ICS use versus non-use in patients with COPD, by the inclusion or exclusion of protopathic and latency time periods, without and with immortal time bias

	Number with events	Person-years	Rate per 1000 per year	Crude HR	Adjusted* HR (95% CI)
No immortal time bias					
No latency and no protopathic periods					
None (reference)	740	132,764	5.6	1.00	1.00 (Reference)
Any ICS	778	172,270	4.5	1.05	1.08 (0.97-1.20)
No latency and one-year protopathic period					
None (reference)	331	131,048	2.5	1.00	1.00 (Reference)
Any ICS	623	171,542	3.6	1.17	1.19 (1.04 -1.37)
One-year latency and no protopathic period					
None (reference)	1011	168,741	6.0	1.00	1.00 (Reference)
Any ICS	507	136,293	3.7	0.92	0.94 (0.82-1.08)
One-year latency and one-year protopathic period					
None (reference)	447	166,296	2.7	1.00	1.00 (Reference)
Any ICS	507	136,293	3.7	0.92	0.94 (0.81-1.07)
With immortal time bias					
No latency and no protopathic periods					
None (reference)	740	87,092	8.5	1.00	1.00 (Reference)
Any ICS	778	217,942	3.6	0.45	0.46 (0.41-0.51)
No latency and one-year protopathic period					
None (reference)	331	85,526	3.9	1.00	1.00 (Reference)
Any ICS	623	217,063	2.9	0.67	0.68 (0.59-0.78)
One-year latency and no protopathic period					
None (reference)	1011	99,744	10.1	1.00	1.00 (Reference)
Any ICS	507	205,290	2.5	0.26	0.26 (0.23-0.29)
One-year latency and one-year protopathic period					
None (reference)	447	97,299	4.6	1.00	1.00 (Reference)
Any ICS	507	205,290	2.5	0.47	0.48 (0.42-0.55)

FIGURE LEGENDS

Figure 1 Flowchart of the study cohort formation.

Figure 2 Adjusted hazard ratio of lung cancer incidence (solid line) and 95% confidence intervals (dashed lines) according to time since first ICS prescription, fit by cubic splines. Graph starts at one year because of the one-year latency period.

Figure 3 Adjusted hazard ratio of lung cancer incidence (solid line) and 95% confidence intervals (dashed lines) according to mean daily dose (in fluticasone equivalents), fit by cubic splines.
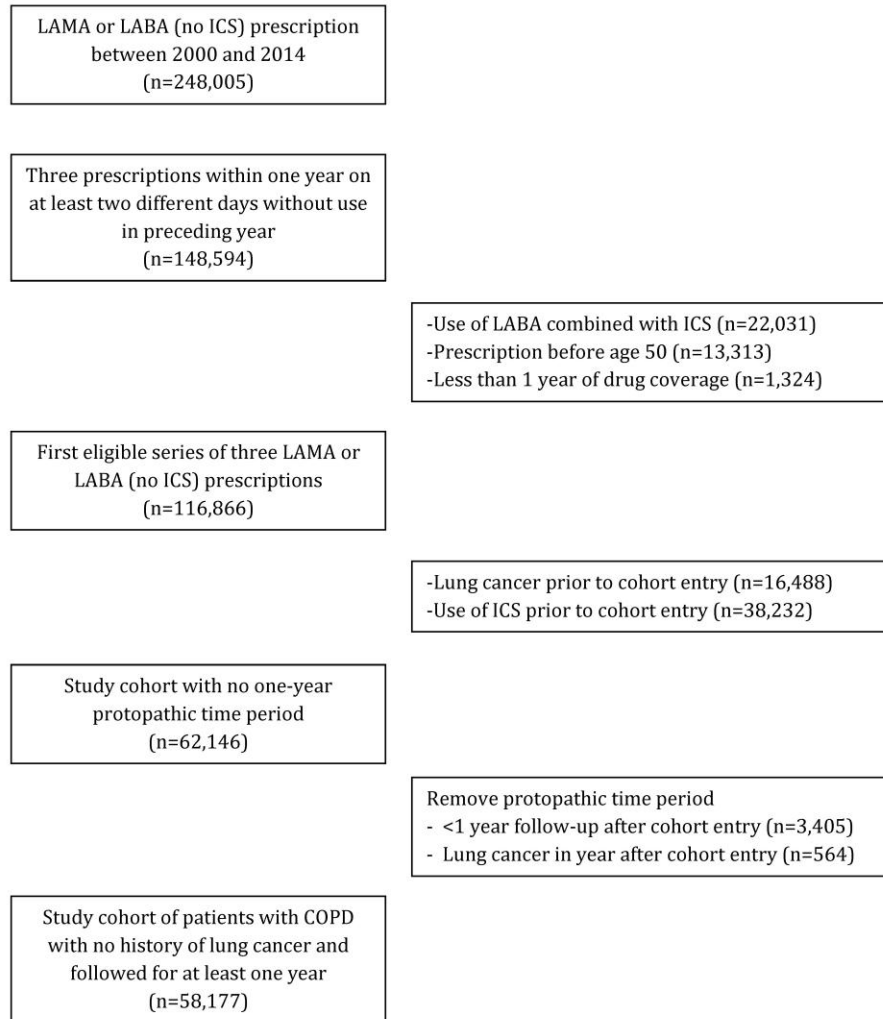
Figure 1

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┌─────────────────────────────────┐
│ LAMA or LABA (no ICS) prescription │
│        between 2000 and 2014       │
│           (n=248,005)              │
└─────────────────────────────────┘

┌─────────────────────────────────┐
│ Three prescriptions within one year on │
│ at least two different days without use │
│        in preceding year           │
│           (n=148,594)              │
└─────────────────────────────────┘
                                    ┌──────────────────────────────────────┐
                                    │ -Use of LABA combined with ICS (n=22,031) │
                                    │ -Prescription before age 50 (n=13,313)    │
                                    │ -Less than 1 year of drug coverage (n=1,324) │
                                    └──────────────────────────────────────┘
┌─────────────────────────────────┐
│  First eligible series of three LAMA or │
│    LABA (no ICS) prescriptions     │
│           (n=116,866)              │
└─────────────────────────────────┘
                                    ┌──────────────────────────────────────┐
                                    │ -Lung cancer prior to cohort entry (n=16,488) │
                                    │ -Use of ICS prior to cohort entry (n=38,232)  │
                                    └──────────────────────────────────────┘
┌─────────────────────────────────┐
│   Study cohort with no one-year    │
│      protopathic time period       │
│           (n=62,146)               │
└─────────────────────────────────┘
                                    ┌──────────────────────────────────────┐
                                    │ Remove protopathic time period        │
                                    │ - <1 year follow-up after cohort entry (n=3,405) │
                                    │ - Lung cancer in year after cohort entry (n=564) │
                                    └──────────────────────────────────────┘
┌─────────────────────────────────┐
│  Study cohort of patients with COPD │
│  with no history of lung cancer and │
│     followed for at least one year  │
│           (n=58,177)               │
└─────────────────────────────────┘
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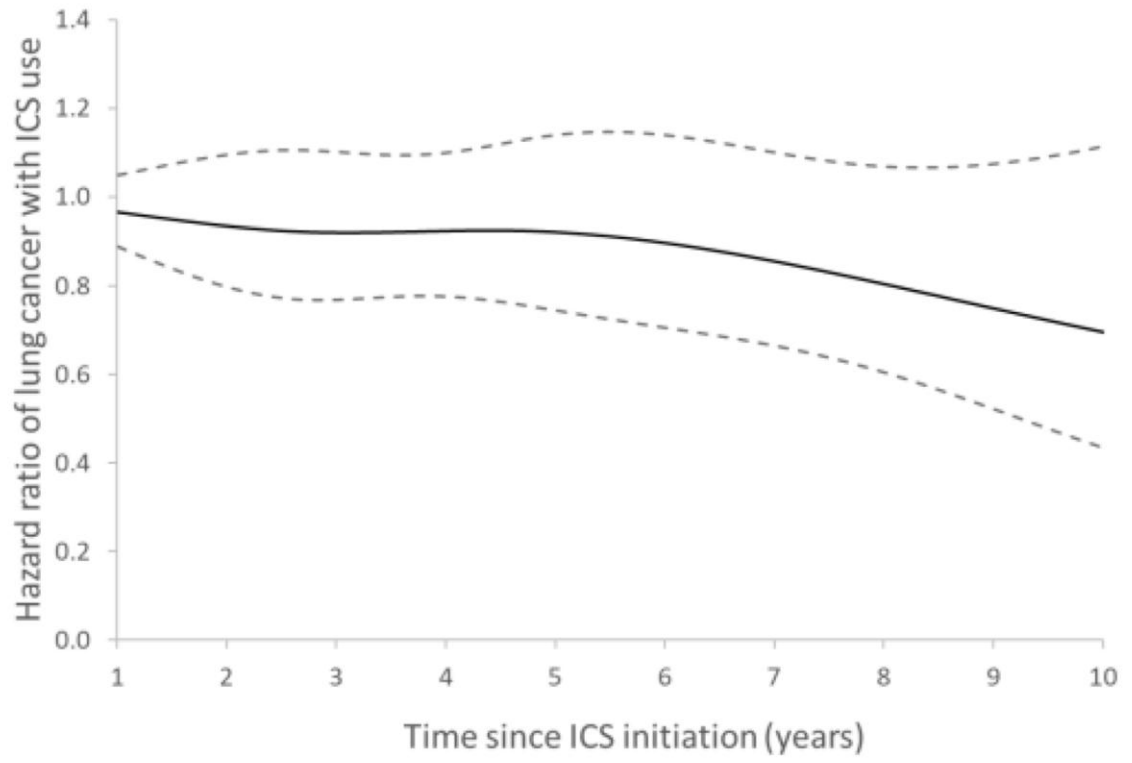
Figure 2

Figure 3