



Inhaled corticosteroids and risk of lung cancer among chronic obstructive pulmonary disease patients: a comprehensive analysis of nine prospective cohorts

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Background: It remains uncertain whether there is a protective effect of inhaled corticosteroids (ICs) against lung cancer in chronic obstructive pulmonary disease (COPD) patients.

Methods: Databases including PubMed, Web of Science, EMBASE, and Medline were comprehensively searched. Random-effects model meta-analysis was conducted to calculate the hazard ratios (HRs) for lung cancer incidence among ICs users versus non-ICs users in patients with COPD. Stratified analysis was performed based on region and age of each study. This review was registered on PROSPERO (registration number CRD42020159082).

Results: Based on data from 181,859 COPD patients with a total follow-up duration of 1,109,339.9 person-years, we identified that the use of ICs in COPD patients was associated with a decreased risk of lung cancer [HR: 0.73, 95% confidence interval (CI): 0.62–0.86; $P < 0.001$]. The region-specific HRs for lung cancer incidence were 0.62 (95% CI: 0.62–0.86; $P = 0.004$), 0.77 (95% CI: 0.60–0.97; $P = 0.028$) and 0.81 (95% CI: 0.61–1.08; $P = 0.155$) among European, Asian and North American COPD patients, respectively. Additionally, we found the consistent outcome among age groups (≥ 70 years old: HR: 0.73, 95% CI: 0.65–0.99, $P = 0.043$; < 70 years old: HR: 0.74, 95% CI: 0.56–0.99, $P = 0.040$).

Conclusions: This study demonstrates that ICs have a protective effect against lung cancer in COPD patients. It could provide guidance for clinicians in the prevention of lung cancer among patients with COPD.

Keywords: Inhaled corticosteroids; chronic obstructive pulmonary disease; lung cancer; meta-analysis

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Introduction

With a prevalence of 10.2% among people more than 40 years old around the world, chronic obstructive pulmonary disease (COPD) seems to be a rather prevalent respiratory disease (1). COPD is a disease with insidious onsets and a poor prognosis. More than 70% COPD patients are at stage 1 or 2 of Global Initiative for Chronic Obstructive Lung Disease (GOLD), with very mild respiratory symptoms such as Shortness of Breath on Exertion (SOBOE). As a result, few of them would seek medical consultations before acute exacerbation (2,3).

COPD is an inflammatory disease of the respiratory system and is considered as a risky element of lung cancer (4). A comprehensive review of studies reported some possible pathogenic mechanisms to explain the potential association between COPD and lung cancer (5). Other literature suggested that the severity of COPD was positively correlated with the development of lung cancer (6,7). Inflammation is also associated with lung cancer. Some studies found that chronic inflammation was involved at the onset of lung cancer through some mechanisms, which were partially independent of smoking (8,9). Therefore, it is reasonable to carry out some research on early anti-inflammatory therapy in COPD patients to prevent malignant transformation.

Some cohort studies showed that inhaled corticosteroids (ICs) may delay or prevent the incidence of lung cancer to some extent (10-12). Nevertheless, some cohort studies showed that compared with general population, COPD patients using ICs demonstrated an increased risk of lung cancer (13,14). Therefore, the protective effect of ICs for lung cancer in COPD patients was not clear. We performed a systematic review including a meta-analysis to determine the exact effect of ICs of lung cancer in COPD patients. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at: <http://dx.doi.org/10.21037/tlcr-20-1126>).

Methods

Systematic review

PubMed (update to February 2020), EMBASE (from 1980 to February 2020), Web of Science (update to February 2020), and Medline (from 1966 to February 2020)

were comprehensively searched to identify longitudinal epidemiological studies. We amalgamated “inhaled corticosteroids” or “ICs” or “chronic obstructive pulmonary disease” or “COPD” with “lung cancer”, “neoplasm” and “tumor”, along with their Medical Subject Headings (MeSH) terms. In addition, we conducted manual searches of the reference lists originating from materials published in academic conferences and retrieved review articles. We would contact the corresponding authors for supplementary data when important information was missing. All searched results were evaluated according to the PRISMA statement (15). Protocol of this study was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42020159082).

Study selection criteria

Eligible studies were selected according to the following inclusion criteria: (I) designed on the basis of population-based cohort studies of COPD patients; (II) reported the risk of lung cancer in COPD patients taking ICs; (III) crude hazard ratios (HRs) or adjusted HRs ratios and 95% confidence intervals (CIs) could be obtained or directly estimated from the article. Studies met any of the criteria below would be excluded: (I) COPD patients reported to have developed any type of cancer before using ICs; (II) lack of available data with appropriate statistics, such as study only reported the risk of lung cancer in COPD patients who used different doses of ICs and did not report the overall risk of lung cancer in COPD patients using ICs; (III) case series and case reports; (IV) not written in English.

Data extraction and quality assessment

Three authors (FG, ZH, YF) extracted the data independently and any divergence resolved by consensus. Following information was recorded: the first author's name, country, study period and publication year, sources of COPD patients, number of COPD patients taking ICs, number of COPD patients not taking ICs, median follow-up duration (years), mean or median age of COPD patients (years), crude HRs or adjusted HRs with 95% CIs, and the confounders that the HRs has adjusted.

The Newcastle Ottawa Scale (NOS) was used to evaluate the methodological quality of the selected studies (16) (*Table 1*), including selection (4 items), comparability (1 item), and outcome (3 items). Any disagreement was

Table 1 Demographic details of the included studies

Study	Region	COPD patients		Male, %ICS/ non-ICS	Median/Mean age (years) ICS/non-ICS	Mean follow-up time (years)	NOS score	Data Sources
		Total	ICs/non-ICs					
Kiri <i>et al.</i> , 2009	UK	1,579	127/1,470	63.8/64.5	70.7/70.8	NA	7	1989–2003 the UK General Practice Research Database
Wu <i>et al.</i> , 2016	China	44,048	8,813/35,235	69.0/69.0	65.0/65.0	NA	8	2003–2010 Taiwan National Health Insurance Research Database
Liu <i>et al.</i> , 2017	China	13,686	1,290/12,396	NA	NA	10.2	9	1997–2009 Taiwan National Health Insurance Research Database
Lee <i>et al.</i> , 2018	Korea	1,325	265/1,060	77.0/78.0	63.9/63.7	4.0	9	2002–2013 Korea National Health Insurance Research Database
Sandelin <i>et al.</i> , 2018	Sweden	19,894	NA	NA	NA	NA	8	1999–2009 Primary Care Medical Database and mandatory Swedish National Registers Database
Sorli <i>et al.</i> , 2018	Norway	3,041	1,095/1,946	53.0/57.0	72.0/70.0	NA	9	1995–1997 Nord-Trøndelag Health Study Database and The Cancer Registry of Norway Database
Husebo <i>et al.</i> , 2019	Norway	433	NA	59.6/54.1	63.5/63.5	NA	8	2006–2009 Bergen COPD Cohort Study Database
Raymakers <i>et al.</i> , 2019	Canada	39,676	NA	46.6/46.6	70.7/70.7	5.2	8	1997–2007 Columbia Population-based linked administrative Database
Suissa <i>et al.</i> , 2019	Canada	58,177	36,718/21,459	49.9/55.5	71.1/72.3	4.9	9	2000–2014 Quebec Health Care Databases

COPD, chronic obstructive pulmonary disease; ICs, inhaled corticosteroids.

resolved by consensus.

Statistical analysis

Dichotomous data were extracted using crude HRs or adjusted HRs with 95% CIs. We restricted analyses to studies that adjusted for at least three of the following known confounders: age, gender, body mass index, smoking situation, socioeconomic status, and comorbidities. Adjusted HRs were used in preference wherever available. To avoid the potential heterogeneity existed between studies, we used random-effects model to synthesize HRs and 95% CIs for ICs users versus non-ICs users to determine the risk of lung cancer. Cochran's Q test and the I^2 statistic were used to assess the heterogeneity. Significant heterogeneity was considered in pooled statistics when P-value ≤ 0.05 and I^2 statistic $\geq 50\%$. Stratified analysis based on patients' age (70 years or older, <70 years) and region (Europe, Asia, North America) were carried out. Additionally, we performed sensitivity analyses after the sequential removal of each

study. Publication bias was evaluated by conducting Begg's test and Egger's test, and significant publication bias was set as P value < 0.05 . All analyses were conducted using STATA 15.0 software (STATA Corp, College Station, TX, USA). All the P values were 2-tailed; statistical significance was set as P value < 0.05 .

Results

Study selection

Our search identified 816 potentially eligible published studies. 225 of them were excluded after screening the title and abstract. 45 articles were excluded because the data were not displayed in a suitable format for synthesis. Finally, 9 studies (11-14,17-21) met the inclusion criteria and were included in the meta-analysis (*Figure 1*).

Study characteristics

All 9 studies were prospective cohorts from different

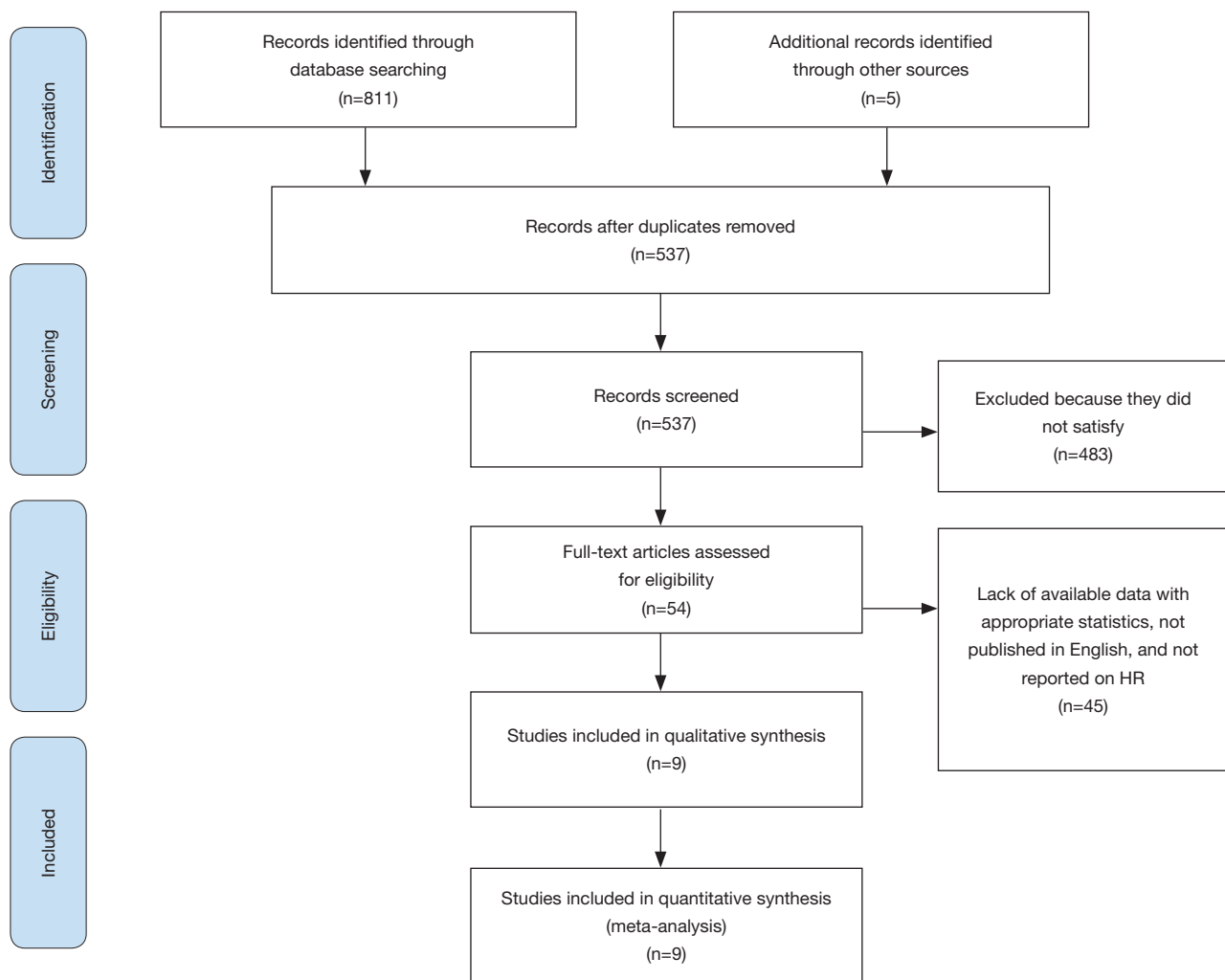


Figure 1 PRISMA diagram of study selection.

countries, including one in UK (11), two in China (17,18), one in South Korea (19), one in Sweden (20), two in Norway (12,14), and two in Canada (13,21). Demographic details of the included studies and the data source of included COPD patients is shown in *Table 1*. Of noted, the included 181,859 COPD patients were followed up for a total of 1,109,339.9 person-years, with a mean follow-up duration of 6.1 years (range, 4.0–10.2 years). The mean age was 68.1 (range, 63.5–71.1) and 68.0 (range, 63.5–72.3) in patients with and without the use of ICs, respectively.

Risk of lung cancer in ICs users

A pooled analysis of 9 studies found that ICs have a

protective effect against lung cancer in COPD patients (HR: 0.73, 95% CI: 0.62–0.86; $P < 0.001$). *Figure 2* shows the individual and overall HR measures.

Remarkable heterogeneity existed ($I^2 = 64.4\%$, $P_{\text{heterogeneity}} = 0.004$) in the pooled analysis. When stratified by patients age, the HRs for lung cancer were 0.80 (95% CI: 0.65–0.99, $P = 0.043$, $I^2 = 71.7\%$, $P_{\text{heterogeneity}} = 0.014$) for patients aged 70 or above and 0.73 (95% CI: 0.54–0.99, $P = 0.040$, $I^2 = 49.6\%$, $P_{\text{heterogeneity}} = 0.137$) for patients who were younger than 70 (*Figure 3*). Additionally, stratification analyses of different regions showed that the HRs for lung cancer were 0.62 (95% CI: 0.45–0.86, $P = 0.004$, $I^2 = 49.5\%$, $P_{\text{heterogeneity}} = 0.114$) for European patients and 0.77 (95% CI: 0.60–0.97, $P = 0.028$, $I^2 = 32.5\%$, $P_{\text{heterogeneity}} = 0.228$) for Asian

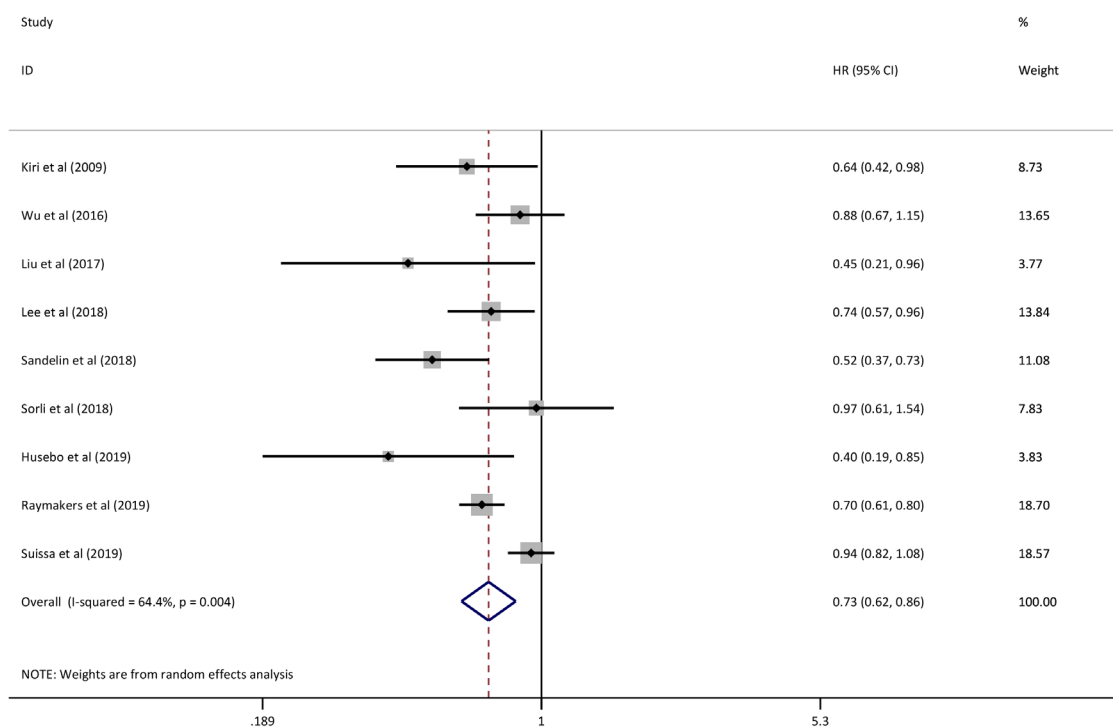


Figure 2 Forest plot of lung cancer risk, showing the hazard ratios (HRs) and 95% confidence intervals (CIs). The squares and horizontal lines correspond to the study-specific HR and 95% CI. The area of the squares reflects the study-specific weight.

patients (Figure 4).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the removal of any of the studies do not influence the results (Table 2). It is worth mentioning that when the study of Suissa (13) was removed, the heterogeneity was eliminated but the result was stable (HR: 0.70, 95% CI: 0.60–0.81; $P < 0.001$), suggesting that the study could be the potential source of inter-study variability. Furthermore, results of Egger's test ($P = 0.191$) or Begg's test ($P = 0.602$, Figure 5) showed no evidence of publication bias for lung cancer analyzed in COPD patients.

Discussion

Our study was aiming at exploring whether ICs have a protective effect against lung cancer in COPD patients. We found that ICs were associated with a decreased risk of lung cancer in patients with COPD and the outcome was consistent among different age groups and region groups.

A previous meta-analysis has shown that ICs reduced

neutrophil and lymphocyte counts in bronchoalveolar lavage fluid from patients with COPD, which suggested that the use of ICs could decrease airway inflammation (22). Therefore, the immunomodulatory effect of ICs on the airways of COPD patients may play an important role in reducing the risk of lung cancer. In recent years, basic studies indicated that COPD may possibly triggered through initial epithelial activation. As the first line defense for external invasion, the epithelial cells act as a barrier to infectious organisms and toxic particles produced from entities (23). Moreover, epithelial cells also produce various antioxidant, antibacterial, anti-protease factors and have tight junctions which could deny any entry of foreign entities and prevent them from damaging or destroying the inner lung mucosa (24,25). In COPD patients, the phlegm-thickened mucus, impaired ciliary function, and chronic exposure to external invasions may cause observable changes to the normal structures of the epithelium (26), which called epithelial–mesenchymal transition (EMT) (27). EMT is a process by which epithelial cells progressively lose cellular polarity and adhesiveness, thus become migratory and assume a mesenchymal phenotype (28–30). The characteristics of

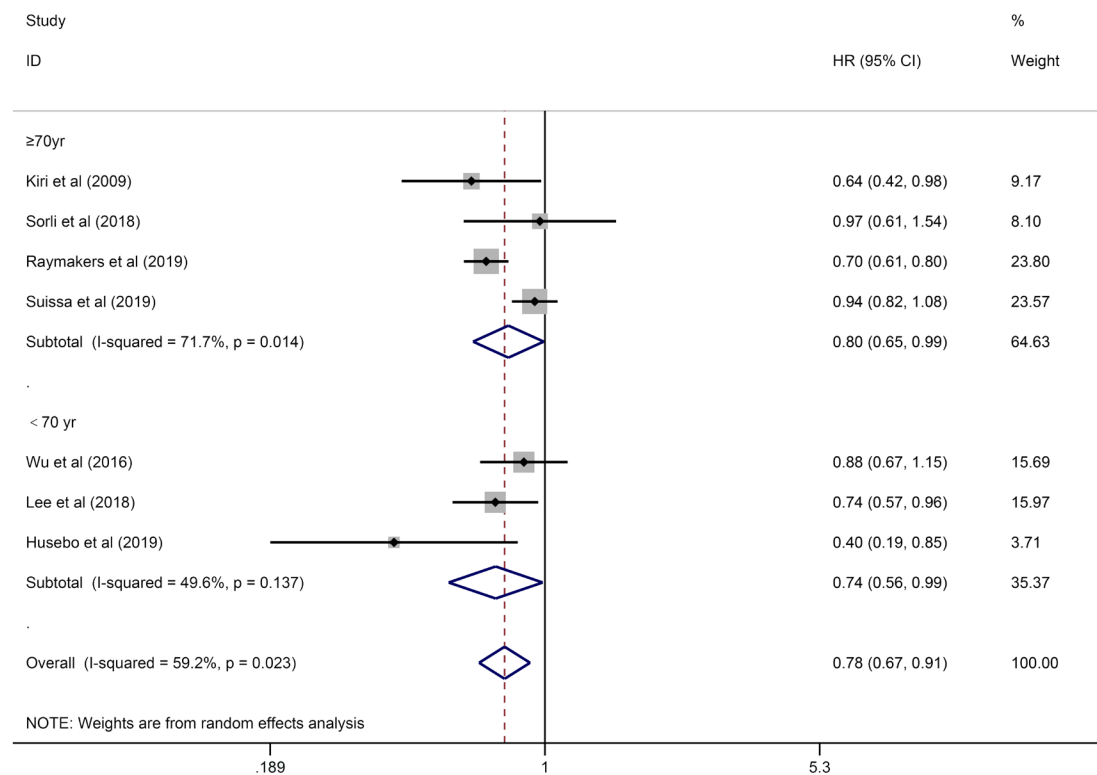


Figure 3 Forest plot of lung cancer risk stratified by age.

EMT are as follows: (I) increased cellular expression of mesenchymal biomarkers such as vimentin and S100A4 (31), which is higher in basal cells especially (32,33); (II) reticular basement membrane (Rbm) fragmentation owing to epithelial matrix metalloprotease (MMP) activity, especially the increase of MMP-9 (collagenase/gelatinase) (31). Additionally, as the prominent feature of EMT, increased Rbm could lead to the formation of a pro-cancer stroma (34). More and more evidence (35-37) has shown that EMT may lead to the elevated risk of lung cancer in patients with COPD. Indeed, epithelia with active EMT are potentially delicate to malignant transformation (38), and EMT in airways of COPD patients may well be the vital bridge between airway fibrosis and cancer development (39). Furthermore, Mahmood *et al.* (40) found that there were strong correlations between the activity of EMT in the leading edge of invasive malignancies and the activity of EMT in the nonmalignant airway areas from which the neoplasm originated. On the other hand, ICs protective effect on lung cancer in COPD patients may also be linked to EMT. Recently, Sohal *et al.* (41) showed that ICs were effective in decreasing mesenchymal expression of vimentin

and S100A4, along with significant reduction in Rbm fragmentation, EGFR and MMP-9 expression in COPD patients. This trial indicated strong suggestive support for ICs' an anti-EMT effect in airways of COPD patients, which may also clarify the links between ICs use and the protection effect against lung cancer in COPD patients.

It is worth mentioning that a dose-response relationship between ICs exposure and lung cancer risk was observed by two studies (10,11), which showed that higher ICs doses were associated with a lower risk of lung cancer. We also noted that it was not a random decision to use ICs or not. ICs would be recommended to those COPD patients who had experienced lots of episodes of acute exacerbation or had forced expiratory volume in 1 second (FEV1) <50% (42). According to recommendations, patients with more severe inflammation or lower FEV1 should consider using ICs. However, lung cancer has been known to be inflammation-associated (43) and related to reduced FEV1 (44). Therefore, although ICs might be in the prescription of patients with high lung cancer risk, lower lung cancer risk was observed in ICs users than non-users in our study, suggesting that ICs had multiple effects in preventing lung

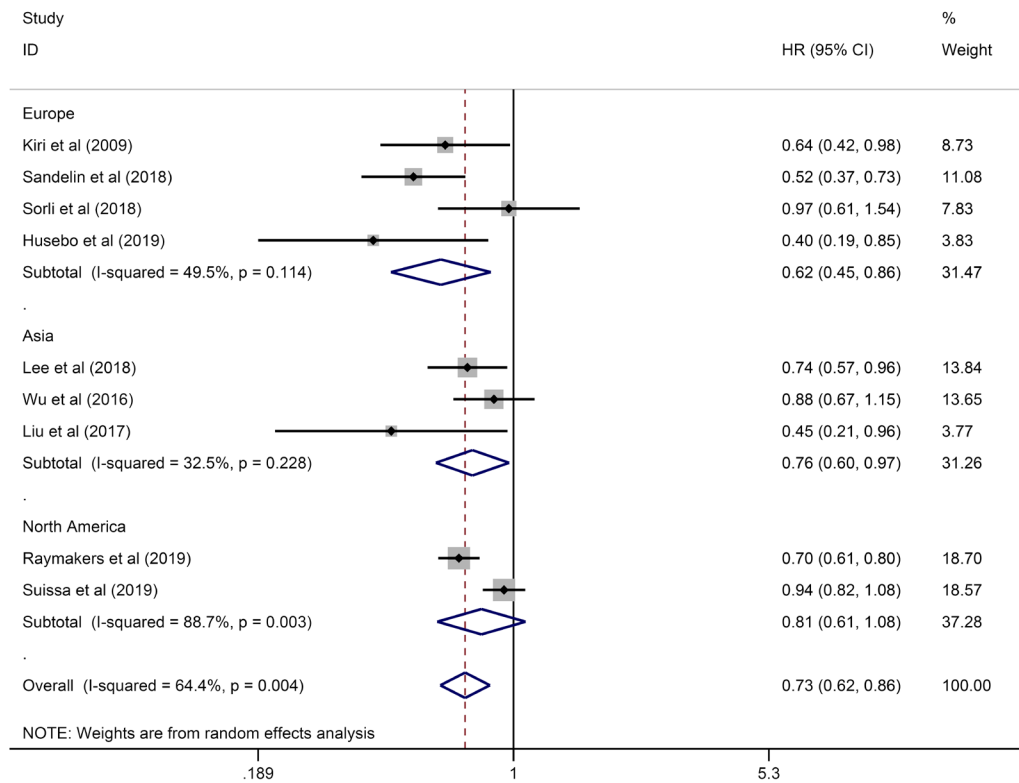


Figure 4 Forest plot of lung cancer risk stratified by region.

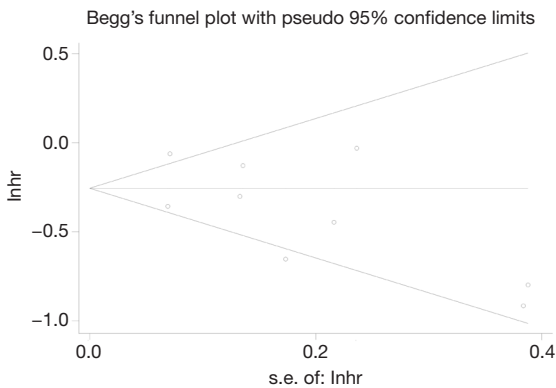


Figure 5 Begg's funnel plot to detect publication bias in overall populations. Each circle represents a separate study for the indicated association.

cancer. Recently, corticosteroids such as budesonide and dexamethasone have been shown to have an inhibitory effect of the proliferation of A549 cells, which is a glucocorticoid-receptor (GR)-rich adenocarcinoma-derived human alveolar epithelial cell line (45). Corticosteroids were thought to

inhibit the retinoblastoma (Rb) phosphorylation to prevent progression from G₁ phase to S phase (45). Another *in vitro* study, Liang (46), showed that the anti-proliferative effect of corticosteroids required functional p53, which plays an essential role in liganded GR repression the NF-κB pathway (47). The NF-κB pathway is constitutively active in most malignancies (48). These studies mainly showed that ICs have an inhibitory effect on GR-rich non-small cell lung cancer (NSCLC) cell lines, which may explain the decreased risk of lung cancer in COPD patients receiving ICs. Furthermore, in mouse models, corticosteroids have been shown to modulate proto-oncogene expression and produce 70% inhibition of lung tumor multiplicity (49).

Three strengths of this study should be highlighted. First, to the best of our knowledge, this is the first meta-analysis to analyze whether the use of ICs in patients with COPD reduces the risk of lung cancer. Second, the included study sample was large and the follow-up time was long enough, hence reducing the likelihood of selection biases. Third, a stratified analysis was performed based on patients' age and region to explore if there were age-based

Table 2 Sensitivity analysis

Study omitted	HR	95% CI	P _{heterogeneity}	I ²	P _{bias}
Kiri <i>et al.</i> , 2009	0.74	0.62, 0.88	0.003	67.7	0.902
Wu <i>et al.</i> , 2016	0.70	0.59, 0.85	0.003	67.4	0.711
Liu <i>et al.</i> , 2017	0.74	0.63, 0.88	0.005	65.8	0.902
Lee <i>et al.</i> , 2018	0.72	0.60, 0.87	0.002	68.7	0.711
Sandelin <i>et al.</i> , 2018	0.77	0.65, 0.90	0.018	58.5	0.711
Sorli <i>et al.</i> , 2018	0.71	0.60, 0.84	0.003	67.5	0.386
Husebo <i>et al.</i> , 2019	0.75	0.64, 0.88	0.007	64.0	0.902
Raymakers <i>et al.</i> , 2019	0.73	0.60, 0.88	0.008	63.5	0.266
Suissa <i>et al.</i> , 2019	0.70	0.60, 0.81	0.120	38.9	0.536
Combined	0.73	0.62, 0.86	0.004	64.4	0.602

HR, hazard ratio; CI, confidence intervals.

and region-based differences.

We acknowledged some limitations in regards to our meta-analysis. First, because of the different methods used to describe the dose-response of ICs in the included studies, we were unable to combine them to determine if there was a dose-response relationship. Second, the included studies did not contain detailed information regarding smoking status (50), drug use (51), sex (52) and occupational exposures (53), all of which might be risk factors for lung cancer and could not be analyzed in this study. Third, due to data limitations, we were unable to collect and analyze the data of different subtypes of lung cancer to explore the influence of tumor properties on the lung cancer risk of COPD patients. Fourth, due to the inclusion of research publications, publication bias was inevitable.

In conclusion, this meta-analysis demonstrates that ICs have a protective effect against lung cancer in COPD patients. Such an association can provide guidance for clinicians in the prevention of lung cancer among patients with COPD.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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