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# The Incidence and Relative Risk for Developing Cancer Among Patients with COPD: A Nationwide Cohort Study in Taiwan

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Abbreviations: COPD = chronic obstructive pulmonary disease; NHI = National Health Insurance; NHIRD = National Health Insurance Research Database; HR = hazard ratio; CI = confidence interval; OR = odds ratio.

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## Abstract

**Objectives:** This observational study aim to exam the incidence of malignant diseases, including specific cancer types, after the diagnosis of COPD in Taiwanese patients. using a nationwide cohort database.

**Setting:** Taiwan's National Health Insurance Research Database.

**Participants:** The definition of a patient with COPD was a patient with a discharge diagnosis of COPD (ICD-9-CM codes: 490-492, 496) or at least three ambulatory visits for COPD and prescribed COPD medications. The index date was the date of the first COPD diagnosis. Patients had a history of malignancy disorders before index date were excluded. In total, 13,470 patients with COPD were retrieved and analyzed. There are 26,940 control subjects without COPD after matching age and gender. They were followed from index date to malignancy diagnosis, death, or the end of study follow up (December 31, 2011), whichever came first.

**Primary outcome measures:** Patients are diagnosed with cancer.

**Results:** The mean age  $\pm$  standard deviation of patients with COPD was 57.90 $\pm$ 13.46 years. The average length of follow-up was 3.87 years. There are 978 patients diagnosed with cancer in patients with COPD. The most common cancer in patients with COPD including: lung cancer, liver cancer, colorectal cancer, breast cancer, prostate cancer, and stomach cancer.

**Conclusions:** The risk of developing cancer is higher in patients with COPD compared the patients without COPD. Cancer screening is warranted in patients with COPD.

## Strengths and limitations of this study

We analyzed the risk of different cancer types in patients with COPD and stratified by disease severity according to the number of prescription drugs. The limitations were lack of COPD severity and cancer staging from the claims database.

**Keywords:** Cancer; chronic obstructive pulmonary disease

## Introduction:

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation which is not fully reversible and the disease is usually progressive and associated with inflammatory response of the lung to noxious particles or gases.<sup>1</sup> The study have shown COPD was the sixth commonest cause of death worldwide in 1990, and it was predicted to become the third commonest cause by 2020.<sup>2</sup> Cigarette smoking is the most common cause of COPD and smoking is also the risk factor of lung cancer. Lung cancer risk increases with decreasing lung function in patients with COPD.<sup>3</sup> The systemic effects of smoking and chronic systemic inflammation response in patients with COPD contribute to the development of respiratory symptoms, functional impairment, chronic comorbidities and including the extra pulmonary cancer.<sup>4</sup> Previous study demonstrated that COPD was associated with an increased risk of both lung cancer mortality and extra pulmonary cancer mortality.<sup>5</sup> In other cohort studies,<sup>4,6-9</sup> patients with COPD increased mortality and risk of extra pulmonary cancers. Some of these studies were limited in number or study in a local hospital and all of them without mention of specific

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4 type of extra pulmonary cancer. The aim of this study was to exam the  
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6 incidence of malignant diseases, including specific cancer types, after the  
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8 diagnosis of COPD compared patients without COPD in Taiwanese  
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10 patients, using a nationwide cohort database.  
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## 12 13 14 **Material and Methods:**

### 15 16 *Ethics Statement*

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18 This study was conducted by using unidentifiable claims database  
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20 provided by the National Health Insurance and the principal investigator  
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22 was requested to sign the agreement upon compliance with the  
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24 Computer-Processed Personal Data Protection Act during proposal  
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26 application. In addition, the policy of our institution review board is  
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28 consistent with the principles of the Declaration of Helsinki. This study  
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30 was approved by the Institutional Review Board of the Chi Mei Medical  
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32 Center (IRB no. 10405-E03).  
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### 39 40 *Source of data*

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42 Taiwan launched a single-payer National Health Insurance (NHI)  
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44 program in 1995. The National Health Insurance Research Database  
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46 (NHIRD), a medical claims database, was established and released for  
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48 research purposes. The NHIRD contains all inpatient and outpatient  
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50 claims data in Taiwan, including patients' demographic characteristics,  
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52 dates of clinical visits, disease diagnoses, prescription medications, and  
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54 expenditure amounts. More than 99% of the total population in Taiwan  
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56 was enrolled in the NHI Program. In this study, we analyzed the claim  
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3 data of one million beneficiaries (from January 1, 2000 to December 31,  
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5 2011) randomly sampled from all of the beneficiaries registered in 2000.  
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### 9 10 *Study groups*

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12 In the present study, the definition of a patient with COPD was a  
13 patient with a discharge diagnosis of COPD (ICD-9-CM codes: 490-492,  
14 496) or at least three ambulatory visits for COPD and prescribed COPD  
15 medications, including short acting  $\beta_2$  agonists (SABA), long acting  $\beta_2$   
16 agonists (LABA), theophyllines, inhaled corticosteroids (ICS),  
17 short-acting muscarinic antagonists (SAMA), Long-acting muscarinic  
18 antagonists (LAMA), combination inhaled corticosteroid/long-acting $\beta_2$   
19 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC).  
20 Patients with COPD was diagnosed between January 1, 2000 and  
21 December 31, 2010 and older than 40 years. The index date was the date  
22 of the first COPD diagnosis. Patients had a history of malignancy  
23 disorders (ICD-9-CM codes 140 to 208) before index date were excluded.  
24 During the study period, more than one readmission events may have  
25 occurred for the same patient; only the data from the first-time  
26 hospitalization record for COPD was analyzed to ensure the  
27 independence of observations. In total, 13,470 patients with COPD were  
28 retrieved and analyzed.  
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49 The control subjects were selected from the remaining patients without  
50 COPD and no history of malignancy disease before index date and were  
51 matched to the patients with COPD by age and gender. The case: control  
52 ratio was 1:2. In total of 26,940 patients without COPD and malignancy  
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3 disease were selected as controls. Case and control subject were followed  
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5 from index date to malignancy diagnosis, death, or the end of study  
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7 follow up (December 31, 2011), whichever came first.  
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### 10 11 ***Definition of Malignancy cases.***

12 Registry of Catastrophic Illness Database was used in cancer diagnosis. If  
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14 a patient is diagnosed by a physician as a malignancy disease under  
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16 Ministry of Health and Welfare guidelines, the patient can submit related  
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18 information and apply for a catastrophic illness certificate. The  
19  
20 application will be formally reviewed by more than 2 physician. Patients  
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22 with in situ malignancies were excluded because patients with in situ  
23  
24 malignant diseases do not qualify for a catastrophic illness certificate.  
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### 32 ***Comorbidities and medication measures***

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34 Baseline comorbidities were assessed before index date for one year.  
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36 They included chronic kidney disease, liver disease, diabetes, and  
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38 hyperlipidemia. The ICD-9-CM codes used to define each condition. The  
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40 Charlson's index<sup>10,11</sup> predicts the mortality for a patient who has a range  
41  
42 of comorbid conditions and has been adapted for use with the ICD-9-CM  
43  
44 coded administrative database.  
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47 COPD medication use on the index date was recorded. We examined use  
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49 of oral steroid, SABA, LABA, theophyllines, ICS, SAMA, LAMA,  
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51 ICS/LABA, MTX, and AC.  
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### 55 ***Statistics***

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3 We described the demographic characteristics of the patients, including  
4 age, gender, Charlson's comorbidity index, comorbidities and COPD  
5 medications. Continuous variables are presented as the means (standard  
6 deviations (SD)), and discrete variables are presented as counts and  
7 percentages. We used Chi-square tests for comparing categorical  
8 variables and t tests for comparing continuous variables. All of the tests  
9 of significance were 2-tailed, and a P value of <.05 was considered  
10 statistically significant. The statistical significance was inferred at a  
11 two-sided p value of < 0.05. All of the statistical analyses were performed  
12 using the Statistical Analysis Software (SAS) System, version 9.3 (SAS  
13 Institute Inc., Cary, NC, USA).  
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### 30 **Result:**

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32 The characteristics and comorbidities of the study subjects are shown  
33 in Table 1. There are 13,470 patients with COPD enrolled in the study.  
34 The mean age and SD of patients with COPD was 57.9±13.46 years.  
35 Ten-year age groups distribution showed that 29.8% were below 49 years  
36 of age, 37.53% were 50-59 years, 14.83% were 60-69 years, and 17.77%  
37 were 70 years of age or older. The average length of follow-up was 3.87  
38 years from COPD diagnosis to patients with any kind of cancers  
39 compared with 5.04 years in control groups. There are 978 patients  
40 diagnosed with cancer in patients with COPD. The patients with COPD  
41 had a higher prevalence of comorbidities than the control group,  
42 including chronic kidney disease, liver disease, diabetes, and  
43 dyslipidemia.  
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Table 2 show the most common distribution of different kinds of cancer in COPD patients. The risk of developing malignancy was different in men and women. The most common cancer in male patients with COPD in order of frequency were: lung cancer, liver cancer, colorectal cancer, prostate cancer, and esophagus cancer. In patients with COPD and lung cancer, the mean age was 61.65 years (SD:10.4) and mean follow-up duration was 3.9 years. In patients with COPD and liver cancer, the mean age±SD was 60.82±12.55 years with mean (SD) follow-up time of 4.47 (2.84) years. The most common medication used to treat COPD was theophylline with 67.59%, followed by steroid with 38.65%, and SABA with 32.31% and there are 18.81% patients with COPD taking three medicines or more to control symptoms of COPD.

Table 3 showed the adjusted HR of developing cancer in patients with COPD was 2.80 (95% CI 2.55-3.09) compared to patients without COPD after adjusting for age, sex and comorbidities. The adjusted HR of developing cancer in male patients with COPD was 1.26 (95% CI 1.14-1.39) compared to female patients with COPD after adjusting for age, sex and comorbidities. Being elderly is associated with a higher risk of developing cancer (50-59, AHR 1.72 (1.51-1.95); 60-69, AHR 2.43 (2.09-2.82); >70, AHR 1.61 (1.38-1.88). Liver disease and diabetes were associated with a higher risk of developing cancer after adjusting for age, sex and comorbidities.

Table 4 showed the adjusted HR of developing cancer in patients with COPD after adjusting for age, sex comorbidities, and COPD medications. After adjusting for age, sex comorbidities and COPD medications, the

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4 risk of developing cancer in patients with COPD was associated with the  
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6 number of COPD medications compared to patients without COPD. The  
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8 AHR of developing cancer in patients with COPD and used more than 3  
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10 kinds of COPD medication was 1.24 (95% CI 1.05-1.47) compared to  
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12 patients with COPD and only used one kind of COPD medications.  
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15 Figure 1 showed the cumulative incidence rate of any types of cancer  
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17 in patients with or without COPD. Kaplan-Meier analysis was used to  
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19 compare the patients with or without COPD in the length of time after  
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21 index date until first occurrence of the cancer. According to the number of  
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23 medications that are used to treat COPD, we divided patients with COPD  
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25 into three group and Figure 2 showed their cumulative incidence rate of  
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27 any types of cancer in patients with or without COPD.  
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## 32 Discussion

### 33 Cancer type in patients with COPD

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35 This is the first study to show the common type of cancer among  
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37 patients with COPD. The most common 5 cancer after COPD diagnosis  
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39 were: lung cancer, liver cancer, colorectal cancer, prostate cancer and  
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41 esophagus cancer in male patients and lung cancer, breast cancer,  
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43 colorectal cancer, liver cancer and stomach cancer in female patients.  
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45 Patients with COPD had high risk for development of cancer and within a  
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47 short period of time to get cancer compared to non-COPD population.  
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49 Patients with COPD had high prevalence of comorbidities compared to  
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51 the non-COPD population, including chronic kidney disease, liver disease,  
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53 diabetes, and dyslipidemia. Patients with COPD elevated risk of  
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developing cancer when they used more kinds of COPD medications compared the non-COPD population. In patients with COPD, the risk of developing cancer was significant when they used more than 3 kinds of COPD medications compared to the patients with COPD only used 1 kind of COPD medications.

### **Lung cancer and COPD**

Both COPD and lung cancer have high morbidity and mortality worldwide.<sup>12,13</sup> Previous studies<sup>14,15</sup> showed that patients with COPD increased risk for development of lung cancer and lung cancer is an important cause of death in patients with COPD.<sup>16</sup> Chronic inflammation after extracellular stimulation, such as tobacco smoking, occupational and environmental inhalants play a key role in COPD and lung cancer. Thus, shared risk factors and inflammatory pathways lead to the similar pathologic mechanisms of COPD and lung cancer.<sup>17</sup>

### **Liver cancer and COPD**

Alpha1-antitrypsin deficiency is one of the common inherited disorders among white persons and predisposed to COPD, cirrhosis and hepatoma.<sup>18,19</sup> Alpha1-antitrypsin deficiency is not an important cause of childhood liver diseases in Southeast Asian population<sup>20</sup> and is also rare in Taiwan. Liver cancer is one of the most common tumor type in Taiwan because Taiwan is the high prevalence of virus hepatitis, with about 20% of the general population suffering from chronic hepatitis B virus infection and 4.4% of the population with chronic hepatitis C virus

infection.<sup>21</sup>

### Colorectal cancer and COPD

Patients with COPD also have high risk of colorectal cancer. There is a nationwide population-based observed study to investigate the influence of COPD on intensive care unit admissions, medication treatments and mortality following colorectal cancer surgery.<sup>22</sup> The authors identified 7.9% colorectal cancer surgery patients had a COPD diagnosis and more complication noted after surgery, including higher ICU admission rate, received mechanical ventilation treatment more frequently, underwent reoperation, more frequently received inotropes/vasopressors. Thirty-day mortality after surgery was 13.0% in patients with colorectal cancer and COPD and 5.3% in patients with colorectal cancer without COPD.

A study<sup>23</sup> demonstrated that COPD is one of the most common comorbid conditions in patients with colon cancer. The receipt of adjuvant therapy was related to COPD (55.2% vs 61.5% of patients with vs without COPD, respectively; OR, 0.83; 95% CI, 0.70–0.99) but Patients with COPD and colon cancer had survival benefit after receipt of adjuvant therapy. Although COPD appeared to be a barrier to chemotherapy, chemotherapy can provide a survival benefit to patients who had colon cancer with COPD.

In our study, there are 13,470 patients with COPD and 73 colon cancer in male, 42 colon cancer in female were observed during a mean follow-up of 4.11 years. Most cases of colon cancer develop in older people aged 50 to 59 (33.91%) with a mean age of 61.66 years. Many

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3 colorectal cancers can be prevented through regular screening and  
4 screening is also crucial in patients with COPD.  
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### 10 **Prostate cancer and COPD**

11 It has been noted that dysfunctioning hypothalamic–pituitary–gonadal  
12 axis, such as hypogonadotrophic hypogonadism, in patients with COPD.  
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24,25 The correlation between serum levels of testosterone and risk of prostate cancer is still controversial.<sup>26,27</sup> More recently, a study have implicated patients with COPD have a significant reduction in total and free testosterone compared to the control group.<sup>28</sup> The relationship between testosterone level and prostate cancer in patients with COPD need to be further investigated. In our study, more than 80% of prostate cancers are diagnosed in men who are 60 or older. A prostatic specific antigen based screening tests for prostate cancer may be warranted in the elderly male population with COPD.

### 38 **Aerodigestive cancer and COPD**

41 It is widely accepted that smoking is a risk factor for oropharyngeal cancer, esophagus cancer and COPD. In our study, development of cancers of the upper aerodigestive tract, including oropharyngeal and esophagus cancer, also common in patients with COPD. A cohort study among 17,774 men showed a positive association between smoking and subsequent cancers of the upper aerodigestive tract (relative risk, 2.02; 95% CI, 1.01 to 4.06) with evidence of dose-response effects. Regular smoking will increase risk of COPD, aerodigestive tract and lung

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3 cancer.<sup>29</sup> There is a growing recognition of the importance of systematic  
4 examination of the oral cavity, oropharynx and neck which it can detect  
5 pre-cancers and cancers at an early and curable stage in patients with  
6 COPD and smoking history.  
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### 10 **Cancer types in patients with COPD**

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12 Our studies show a positive association between COPD and subsequent  
13 developing cancer. Compared to those without COPD, patients with  
14 COPD had a 55% increased risk for developing cancer (AHR 1.55, 95%  
15 CI, 1.48 to 1.62). In previous study of the incidence of cancer, smoking  
16 increased the risk of cancer of the oropharynx, upper aerodigestive tract,  
17 and lung.<sup>30</sup> From our analysis, in addition to cancer mentioned above,  
18 common cancer types includes liver, colon, and breast cancers that are  
19 diagnosed with the high frequency in the patients with COPD.  
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31 A population-based study<sup>30,31</sup> revealed that 12% of all cancer patients  
32 had COPD at the time of cancer diagnosis, being about 15% in age more  
33 than 65 years. Besides lung cancer, there is no difference of stage at  
34 diagnoses between cancer patients with or without COPD. After using  
35 multivariate Cox-regression model, the survival rate was poor in patients  
36 with COPD, especially for elderly patients with colon, rectum, larynx,  
37 prostate or urinary bladder cancer.  
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### 49 **Limitation**

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51 The major limitation was that some of the data, including a history of  
52 cigarette smoking, pulmonary function degree of dyspnea, COPD severity  
53 and cancer staging were not available from the claims database. We used  
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4 the database to demonstrate that COPD was significantly associated with  
5 a high risk of cancer, regardless of COPD severity. We also divided  
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7 COPD population into 3 group according to the number of medications  
8 that used to treat COPD to represent the COPD severity. After the  
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10 stratification, we find that patients used more COPD medications are at  
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12 higher risk of developing cancer. The study is a nationwide cohort study,  
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14 and we believe that the large number of participants, the comprehensive  
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16 enrollment of patients with COPD and longtime followed up ensure that  
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18 the data are normally distributed and that the results are significant.  
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27 **Contributorship statement:** Chung-Han Ho : acquisition of data,  
28 analysis and interpretation of data; Yi-Chen Chen: acquisition of data,  
29 analysis of data; Jhi-Joung Wang: contributions to conception and design;  
30  
31 Kuang-Ming Liao: drafting the article and final approval of the version to  
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33 be published.  
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38 **Competing interests:** None declared.  
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42 agency in the public, commercial or not-for-profit sectors.  
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45 **Data sharing statement:** No additional data are available.  
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Table 1 Demographic Characteristics and Comorbidities in Patients with/without COPD

	COPD N(%) N=13470	Non-COPD N(%) N=26940	P-value
Sex			
Male	7225(53.64)	14450(53.64)	1.0000
Female	6245(46.36)	12490(46.36)	
Age(years)			
40-49	4024(29.87)	8054(29.90)	0.9999
50-59	5055(37.53)	10101(37.49)	
60-69	1998(14.83)	3999(14.84)	
≥70	2393(17.77)	4786(17.77)	
Mean ±SD	57.90±13.46	57.90±13.46	0.9976
Patients with cancer	978(7.26)	717(2.66)	<0.0001
Time to developing cancer (years)			
Mean ±SD	3.87±3.23	5.04±3.17	<0.0001
Comorbidity			
Chronic kidney disease	229(1.70)	36(0.13)	<0.0001
Liver disease	312(2.32)	71(0.26)	<0.0001
Diabetes	808(6.00)	157(0.58)	<0.0001
Hyperlipidemia	191(1.42)	38(0.14)	<0.0001
Charlson Comorbidity Index	0.48±1.22	0.03±0.31	<0.0001
COPD medications			
1	7633(56.67)	-	-
2	3660(27.17)	-	
>=3	2177(16.16)	-	

SD: standard deviation

Table 2 Characteristics of different kinds of cancer in COPD patients

	Lung cancer	Liver cancer	Colorectal cancer	Breast cancer	Prostate cancer	Stomach cancer	Esophagus cancer	Total cancer
Number (%)	238(24.34)	120(12.27)	115(11.76)	61(6.24)	43(4.40)	42(4.29)	35(3.58)	978(100.00)
Sex								
Male	164(68.91)	91(75.83)	73(63.48)	1(1.64)	43(100)	27(64.29)	34(97.14)	625(63.91)
Female	74(31.09)	29(24.17)	42(36.52)	60(98.36)	0(0.00)	15(35.71)	1(2.86)	353(36.09)
Age(years)								
40-49	33(13.87)	15(12.5)	19(16.52)	25(40.98)	2(4.65)	7(16.67)	5(14.29)	186(19.02)
50-59	96(40.34)	55(45.83)	39(33.91)	28(45.90)	16(37.21)	15(35.71)	19(54.29)	398(40.7)
60-69	52(21.85)	22(18.33)	28(24.35)	5(8.20)	12(27.91)	8(19.05)	7(20.00)	188(19.22)
≥70	57(23.95)	28(23.33)	29(25.22)	3(4.92)	13(30.23)	12(28.57)	4(11.43)	206(21.06)
Mean (±SD)	61.65±12.85	60.82±12.55	61.66±12.80	52.17±8.17	65.73±12.65	63.76±15.36	58.14±10.08	57.90±13.46
Follow-up duration [years; mean±SD]	2.71±3.26	4.47±2.84	4.11±3.05	4.73±3.27	4.66±3.14	2.95±2.73	3.36±3.20	3.87±3.23
Comorbidity								
Chronic kidney disease	2(0.84)	1(0.83)	1(0.87)	0(0.00)	0(0.00)	1(2.38)	1(2.86)	21(2.15)
Liver disease	7(2.94)	18(15)	2(1.74)	0(0.00)	2(4.65)	1(2.38)	3(8.57)	52(5.32)
Diabetes	16(6.72)	16(13.33)	12(10.43)	3(4.92)	1(2.33)	4(9.52)	1(2.86)	80(8.18)
Hyperlipidemia	5(2.1)	2(1.67)	4(3.48)	0(0.00)	1(2.33)	0(0.00)	1(2.86)	18(1.84)
COPD medications								
Steroid	100(42.02)	30(25)	40(34.78)	27(44.26)	23(53.49)	16(38.1)	11(31.43)	378(38.65)
SABA	79(33.19)	41(34.17)	35(30.43)	24(39.34)	11(25.58)	13(30.95)	10(28.57)	316(32.31)
LABA	18(7.56)	11(9.17)	7(6.09)	2(3.28)	4(9.3)	3(7.14)	8(22.86)	86(8.79)
Theophyllines	157(65.97)	92(76.67)	82(71.3)	35(57.38)	31(72.09)	27(64.29)	21(60)	661(67.59)
ICS	4(1.68)	5(4.17)	6(5.22)	3(4.92)	5(11.63)	5(11.9)	4(11.43)	53(5.42)
SAMA	47(19.75)	15(12.5)	21(18.26)	3(4.92)	5(11.63)	5(11.9)	6(17.14)	155(15.85)
LAMA	8(3.36)	2(1.67)	1(0.87)	0(0)	1(2.33)	0(0)	0(0)	15(1.53)
LABA/ICS	11(4.62)	5(4.17)	4(3.48)	2(3.28)	2(4.65)	1(2.38)	1(2.86)	43(4.4)
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medications								
1	117(49.16)	62(51.67)	61(53.04)	37(60.66)	21(48.84)	24(57.14)	21(60)	514(52.56)
2	77(32.35)	40(33.33)	36(31.3)	15(24.59)	7(16.28)	10(23.81)	7(20)	280(28.63)
>=3	44(18.49)	18(15)	18(15.65)	9(14.75)	15(34.88)	8(19.05)	7(20)	184(18.81)

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Table 3. Hazard ratio of developing cancer in relation to baseline characteristics of the study subjects

	Crude HR <sup>a</sup> (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> (95% CI <sup>a</sup> )	P-value
Patients				
COPD	2.91(2.64-3.21)	<0.0001	2.80(2.55-3.09)	<0.0001
Non-COPD	1.00		1.00	
Sex				
Male	1.27(1.16-1.40)	<0.0001	1.26(1.14-1.39)	<0.0001
Female(ref.)	1.00		1.00	
Age(years)				
40-49(ref.)	1.00		1.00	
50-59	1.74(1.53-1.98)	<0.0001	1.72(1.51-1.95)	<0.0001
60-69	2.44(2.10-2.83)	<0.0001	2.43(2.09-2.82)	<0.0001
>70	1.53(1.31-1.78)	<0.0001	1.61(1.38-1.88)	<0.0001
Comorbidity				
Chronic kidney disease	2.24(1.46-3.44)	0.0002	1.03(0.66-1.61)	0.9058
Liver disease	4.04(3.09-5.27)	<0.0001	2.30(1.75-3.03)	<0.0001
Diabetes	2.68(2.15-3.33)	<0.0001	1.42(1.12-1.80)	0.0037
Hyperlipidemia	2.45(1.54-3.89)	0.0002	1.11(0.69-1.78)	0.6805

<sup>a</sup> HR=hazard ratio; CI= confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustment for age, sex, and comorbidities.

Table 4. Hazard ratio of developing cancer in relation to baseline characteristics and COPD medications of the study subjects

	AHR <sup>b</sup> with COPD medications (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> for COPD only (95% CI <sup>a</sup> )	P-value
Patients				
Non-COPD	1.00		-	
COPD with only 1 medication	2.59(2.31-2.91)	<0.0001	1.00	
COPD with 2 medication	2.94(2.56-3.39)	<0.0001	1.13(0.97-1.30)	0.1131
COPD with ≥3 medication	3.29(2.79-3.88)	<0.0001	1.24(1.05-1.47)	0.0127
Sex				
Male	1.26(1.14-1.39)	<0.0001	1.60(1.40-1.83)	<0.0001
Female(ref.)	1.00		1.00	
Age(years)				
40-49(ref.)	1.00		1.00	
50-59	1.71(1.50-1.95)	<0.0001	1.81(1.52-2.15)	<0.0001
60-69	2.41(2.08-2.81)	<0.0001	2.50(2.04-3.07)	<0.0001
>70	1.60(1.37-1.86)	<0.0001	2.16(1.76-2.64)	<0.0001
Comorbidity				
Chronic kidney disease	1.03(0.66-1.61)	0.8915	1.04(0.66-1.62)	0.8700
Liver disease	2.30(1.75-3.03)	<0.0001	2.27(1.71-3.03)	<0.0001
Diabetes	1.39(1.10-1.76)	0.0059	1.33(1.04-1.70)	0.0240
Hyperlipidemia	1.11(0.69-1.78)	0.6768	1.10(0.67-1.79)	0.7098

<sup>a</sup> CI= confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustment for age, sex, and comorbidities.



Figure1. Cumulative incidence rate in patients with COPD vs Non-COPD

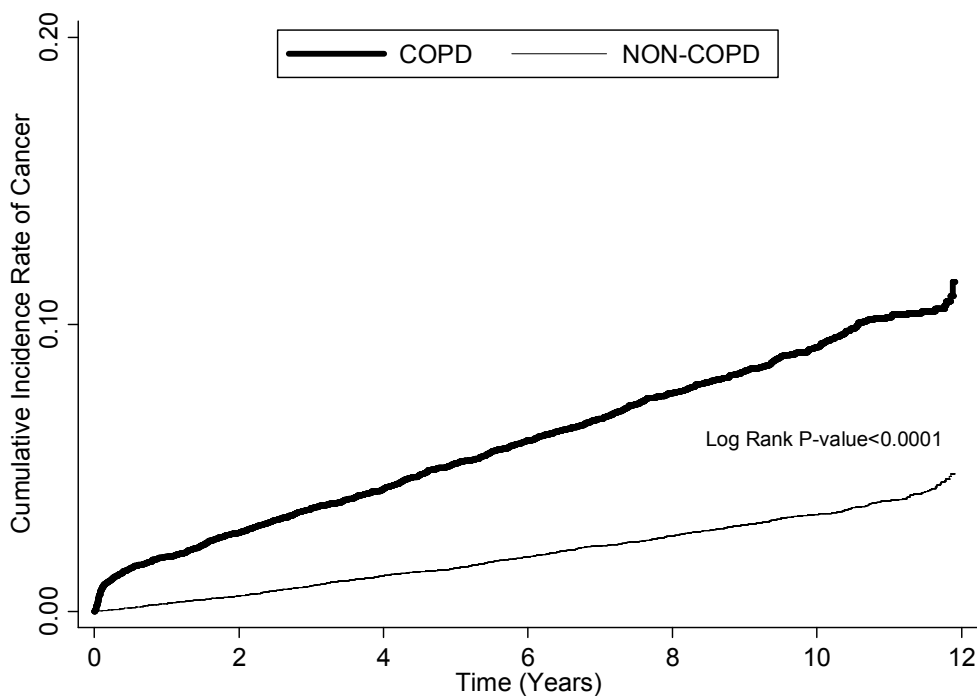
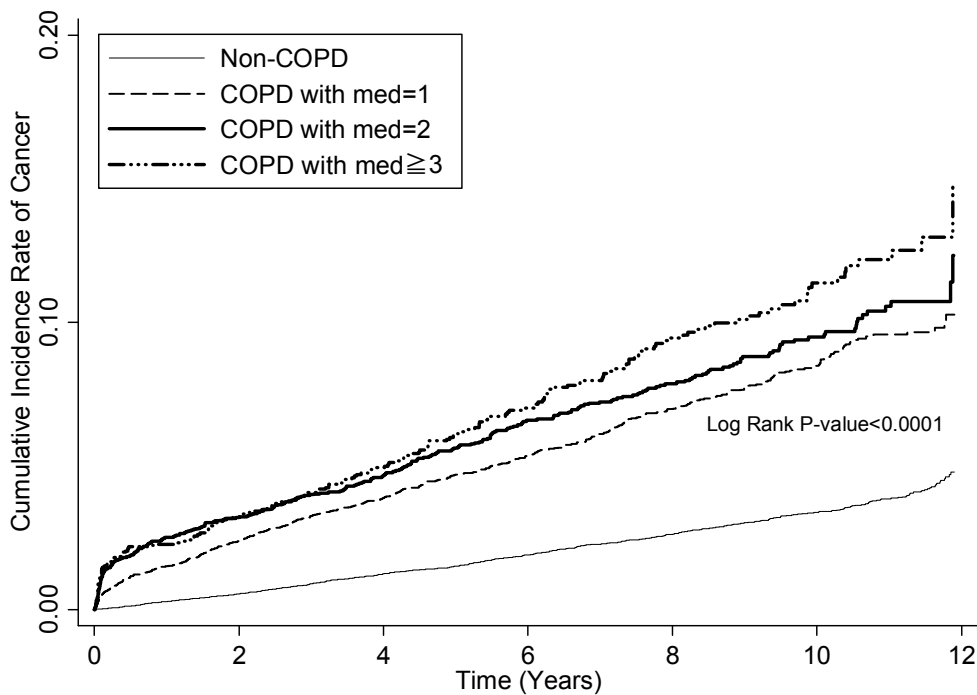


Figure2. Cumulative incidence rate in COPD patients with different medications.



## STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
		(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
Participants	6	<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4,5
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	5
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Study size	10	Describe any efforts to address potential sources of bias	6
Quantitative variables	11	Explain how the study size was arrived at	5,6
Statistical methods	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
		(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5,6
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7,8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(b) Report category boundaries when continuous variables were categorized	7,8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
<b>Other Information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## The Incidence and Relative Risk for Developing Cancer Among Patients with COPD: A Nationwide Cohort Study in Taiwan.

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Keywords:	Chronic airways disease < THORACIC MEDICINE, ONCOLOGY, Epidemiology < THORACIC MEDICINE

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4 **The Incidence and Relative Risk for Developing Cancer**  
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7 **Among Patients with COPD: A Nationwide Cohort Study in**  
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10 **Taiwan**

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Abbreviations: COPD = chronic obstructive pulmonary disease; NHI = National Health Insurance; NHIRD = National Health Insurance Research Database; HR = hazard ratio; CI = confidence interval; OR = odds ratio.

Disclosure: All authors report no disclosures relevant to the manuscript.

## Abstract

**Objectives:** This observational study aimed to examine the incidence of malignant diseases, including specific cancer types, after the diagnosis of chronic obstructive pulmonary disease (COPD) in Taiwanese patients.

**Setting:** Taiwan's National Health Insurance Research Database.

**Participants:** The definition of a patient with COPD was a patient with a discharge diagnosis of COPD or at least three ambulatory visits for COPD. The index date was the date of the first COPD diagnosis. Patients with a history of malignancy disorders before the index date were excluded. In total, 13,289 patients with COPD were analysed. There were 26,578 control subjects without COPD after matching for age and gender. They were followed from the index date to malignancy diagnosis, death, or the end of study follow-up (December 31, 2011), whichever came first.

**Primary outcome measures:** Patients were diagnosed with cancer [n=1681 (4.2%); 973 (7.3%) for COPD patients and 728 (2.7%) for non-COPD patients], and the risk of seven major cancer types, including lung, liver, colorectal, breast, prostate, stomach, and oesophageal cancers, between COPD patients and non-COPD patients was also estimated.

**Results:** The mean age of all study subjects was 57.9±13.5 years. The average length of follow-up to cancer incidence was 3.9 years for COPD patients and 5.0 years for patients without COPD (p<0.01). Patients with COPD were diagnosed with cancer (n=973, 73%) at a significantly higher rate than patients without COPD (n=708, 2.7%)

( $p < 0.01$ ). The hazard ratio for developing cancer in patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients without COPD after adjusting for age, sex, and comorbidities. The most common cancers in patients with COPD included lung, liver, colorectal, breast, prostate, and stomach cancers.

**Conclusions:** The risk of developing cancer is higher in patients with COPD compared with patients without COPD. Cancer screening is warranted in patients with COPD.

### Strengths and limitations of this study

1. We analysed the risk of different cancer types in patients with COPD and stratified them by disease severity according to the number of prescription drugs.
2. The patients with COPD in our study were treated with COPD medications and were over 40 years old. Our study groups were matched by age and gender, and the data were analysed using the Cox model, including patient comorbidities. Our method differed from the standardized incidence ratio, which cannot adjust for comorbidities or medications.
3. This study was a nationwide cohort study with a large number of participants, comprehensive enrolment of patients with COPD, and long-term follow up.
4. The limitations included lack of COPD severity information and cancer staging from the claims database.
5. The data lacked consideration of other factors associated with COPD and cancer, such as lifestyle choices, physical activity, and socioeconomic status.

**Keywords:** Cancer; chronic obstructive pulmonary disease

## Introduction:

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible, and the disease is usually progressive and associated with lung inflammatory responses to noxious particles or gases.[1] COPD was the sixth most common cause of death worldwide in 1990, and it was predicted to become the third most common cause by 2020.[2] Cigarette smoking is the most common cause of COPD, and smoking is a risk factor for lung cancer. Lung cancer risk increases with decreasing lung function in patients with COPD.[3] The systemic effects of smoking and chronic systemic inflammation responses in patients with COPD contribute to the development of respiratory symptoms, functional impairment, and chronic comorbidities and include extra-pulmonary cancers.[4] A previous study demonstrated that COPD was associated with an increased risk of both lung cancer mortality and extra-pulmonary cancer mortality.[5] In other cohort studies,[4-8] patients with COPD had increased mortality and risk of extra-pulmonary cancers. However, previous studies have been limited by few participants or studying only populations at local hospitals, and none of the other studies mention specific types of extra-pulmonary cancers. The aim of this study was to use a nationwide cohort database to examine the incidence of malignant diseases, including specific cancer types, in Taiwanese patients after diagnosis with COPD compared with Taiwanese patients without COPD.

## Materials and Methods:



### ***Ethics statement***

This study was conducted using an unidentifiable claims database provided by the National Health Insurance (NHI), and the principal investigator was requested to sign an agreement regarding compliance with the Computer-Processed Personal Data Protection Act during the proposal application. In addition, the policy of our institutional review board (IRB) is consistent with the principles of the Declaration of Helsinki. This study was approved by the IRB of the Chi Mei Medical Center (IRB no. 10405-E03).

### ***Source of data***

Taiwan launched a single-payer NHI program in 1995. The National Health Insurance Research Database (NHIRD), a medical claims database, was established and released for research purposes. The NHIRD contains all inpatient and outpatient claims data in Taiwan, including patients' demographic characteristics, dates of clinical visits, disease diagnoses, prescription medications, and expenditure amounts. More than 99% of the total population of Taiwan was enrolled in the NHI Program. In this study, we analysed the claim data of one million beneficiaries (from January 1, 2000 to December 31, 2011) randomly sampled from all of the beneficiaries registered in 2000.

### ***Study groups***

In the present study, the definition of a patient with COPD was a patient with a discharge diagnosis of COPD (ICD-9-CM codes: 490-492,

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4 496) or at least three ambulatory visits for COPD who was also  
5 prescribed COPD medications, including short acting  $\beta$ 2 agonists  
6 (SABA), long-acting  $\beta$ 2 agonists (LABA), theophylline, inhaled  
7 short-acting muscarinic antagonists (SAMA), long-acting muscarinic  
8 antagonists (LAMA), combination inhaled corticosteroid/long-acting  $\beta$ 2  
9 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC).  
10 Included patients were those over 40 years of age who received a  
11 diagnosis of COPD between January 1, 2000 and December 31, 2010.  
12 The index date was the date of the first COPD diagnosis. Patients with a  
13 history of malignancy disorders (ICD-9-CM codes 140 to 208) before the  
14 index date were excluded. During the study period, more than one  
15 readmission event may have occurred for the same patient; only the data  
16 from the first-time hospitalization record for COPD were analysed to  
17 ensure the independence of observations. In total, 13,289 patients with  
18 COPD were retrieved and analysed.

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36 The control subjects were selected from the remaining patients without  
37 COPD and with no history of malignancy before the index date. Patients  
38 who were treated with any of the above COPD medications were also  
39 excluded. Considering that cancer was a rare event and a stratified  
40 analysis for seven cancer types was used in our study, patients with  
41 COPD were matched 1:2 for age and gender to the control subjects  
42 without COPD. In total, 26,578 patients without COPD or malignancy  
43 were selected as controls. Case and control subjects were followed from  
44 the index date to malignancy diagnosis, death, or the end of study  
45 follow-up (December 31, 2011), whichever came first.  
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### ***Definition of malignancy cases***

The Registry of Catastrophic Illness Database was used in cancer diagnosis. When a patient is diagnosed by a physician as having a malignancy, under Ministry of Health and Welfare guidelines, the patient can submit related information and apply for a catastrophic illness certificate. The application is formally reviewed by more than two physicians. Patients with in situ malignancies were excluded from this study because patients with in situ malignancies do not qualify for a catastrophic illness certificate.

### ***Comorbidities and medication measures***

Baseline comorbidities were assessed for one year before the index date. They included chronic kidney disease, liver disease, diabetes, and hyperlipidaemia and were recognized by the ICD-9-CM codes used to define each condition. COPD medication use on the index date was recorded. We examined the use of oral steroids, SABA, LABA, theophylline, ICS, SAMA, LAMA, ICS/LABA, MTX, and AC. For estimating the effect of the number of COPD medications, COPD patients in our study were divided into three groups: only one type of COPD medication, two types of COPD medication, and more than three types of COPD medication.

### ***Statistical analysis***

We described the demographic characteristics of the patients, including

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3 age, gender, Charlson comorbidity index, comorbidities, and COPD  
4 medications. Continuous variables are presented as the means with  
5 standard deviations (SD), and discrete variables are presented as counts  
6 and percentages. Chi-square test was used for comparing categorical  
7 variables, and the differences among continuous variables were compared  
8 using Student's t test. The proportion of cancer patients was plotted by  
9 Kaplan-Meier curves with log-rank test for comparing the differences  
10 between COPD and non-COPD patients. The relative risk of cancer was  
11 estimated by Cox proportional regression analysis, which was adjusted  
12 for potential confounding variables, such as age, sex, and comorbidities.  
13 The statistical significance was inferred at a two-sided p value of <0.05.  
14 All of the statistical analyses were performed using the Statistical  
15 Analysis Software (SAS) System, version 9.4 (SAS Institute Inc., Cary,  
16 NC, USA). Kaplan-Meier curves were plotted using Stata 12 (Stata Corp.,  
17 College Station, TX, USA).

## 38 **Result:**

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40 The characteristics and comorbidities of the study subjects are shown  
41 in Table 1. Overall, 13,470 patients with COPD enrolled in the study. The  
42 mean age $\pm$ SD of the COPD patients was 57.9 $\pm$ 13.5 years. A ten-year age  
43 group distribution showed that 29.7% were 49 years of age or younger,  
44 37.6% were 50-59 years, 14.9% were 60-69 years, and 17.8% were 70  
45 years of age or older. The average length of follow-up was 3.9 years from  
46 COPD diagnosis to patients being diagnosed with any type of cancers  
47 compared with 5.0 years in the control groups (p<0.01). Patients with  
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4 COPD were diagnosed with cancer (n=973, 73%) at significantly higher  
5 rates than patients without COPD (n=708, 2.7%) (p<0.01). The patients  
6 with COPD had a higher prevalence of comorbidities than the control  
7 group (p<0.01), including cardiovascular disease, chronic kidney disease,  
8 liver disease, diabetes, and dyslipidaemia.  
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15 Figure 1 shows the cumulative incidence rate of any type of cancer in  
16 patients with or without COPD from the index date until the first  
17 occurrence of the cancer using Kaplan-Meier methods. The patients with  
18 COPD had higher cancer incidence rates compared with patients without  
19 COPD (log-rank test: p<0.01). Table 2 shows that the adjusted HR of  
20 developing cancer among patients with COPD was 2.8 (95% CI: 2.6-3.1)  
21 compared to patients without COPD after adjusting for age, sex, and  
22 comorbidities. For comparing the risk of cancer among each of the seven  
23 cancer types between COPD and non-COPD patients, the adjusted hazard  
24 ratios for each cancer type are reported in Figure 2. Patients with COPD  
25 had significantly higher risks of lung (AHR: 11.6; 95% C.I.: 6.2-21.9),  
26 liver (AHR: 5.0; 95% C.I.: 2.4-10.4), colorectal (AHR: 3.0; 95% C.I.:  
27 1.7-5.2), prostate (AHR: 4.9; 95% C.I.: 1.8-13.5), and oesophageal (AHR:  
28 6.0; 95% C.I.: 1.1-32.7) cancer. Moreover, the stratified analysis of the  
29 cancer risk between COPD and non-COPD patients by age group and sex  
30 for any type of cancer and each of the seven cancer types is also  
31 presented (Figure 2).  
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52 Patients with COPD were divided into three groups according to the  
53 number of medications used to treat COPD, and Figure 3 shows the  
54 cumulative incidence rates of any type of cancer in patients with or  
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without COPD. Patients had a higher risk of developing cancer when more bronchodilator medications were used.

Table 3 shows the adjusted HR of developing cancer in patients with COPD who were taking multiple COPD medications compared with non-COPD patients or COPD patients who were treated with only one COPD medication after adjusting for age, sex, and comorbidities. COPD patients who were treated with COPD medications had a 2.6-fold (95% C.I.: 2.3-3.0), 3.0-fold (95% C.I.: 2.6-3.4), and 3.3-fold (95% C.I.: 2.8-3.9) risk of any types of cancer for one, two, and more than three medication treatments, respectively, compared with patients without COPD. The AHR of developing cancer among patients with COPD who used more than three types of COPD medication was 1.2 (95% C.I.: 1.0-1.5) compared to patients with COPD who only used one type of medication. In addition, the adjusted HR of developing cancer was 1.6 (95% C.I.: 1.4-1.8) in male COPD patients compared to female COPD patients after adjusting for age and comorbidities. Being elderly was associated with a higher risk of developing cancer [50-59, AHR: 1.8 (95% C.I.: 1.5-2.2); 60-69, AHR: 2.5 (95% C.I.: 2.1-3.1); >70, AHR: 2.2 (95% C.I.: 1.8-2.7)]. Liver disease and diabetes were associated with a higher risk of developing cancer after adjusting for age, sex, and comorbidities [liver disease, AHR: 2.3 (95% C.I.: 1.7-3.1); diabetes, AHR: 1.3 (95% C.I.: 1.0-1.7)].

## Discussion

### Cancer type in patients with COPD

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4 This is the first study to show the common types of cancer among  
5 patients with COPD. The five most common cancers after COPD  
6 diagnosis included: lung cancer, liver cancer, colorectal cancer, prostate  
7 cancer, and oesophageal cancer in male patients and lung cancer, breast  
8 cancer, colorectal cancer, liver cancer, and stomach cancer in female  
9 patients. Patients with COPD had a higher risk of developing cancer and  
10 developed cancer within a shorter period of time compared with the  
11 non-COPD population. Patients with COPD had a high prevalence of  
12 comorbidities compared to the non-COPD population, including chronic  
13 kidney disease, liver disease, diabetes, and dyslipidaemia. Patients with  
14 COPD had an elevated risk of developing cancer when they used more  
15 types of COPD medications compared with the non-COPD population. In  
16 patients with COPD, the risk of developing cancer was significant when  
17 they used more than three types of COPD medications compared to the  
18 COPD patients who only used one type of COPD medication.  
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### 38 **Lung cancer and COPD**

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40 Both COPD and lung cancer have high morbidity and mortality rates  
41 worldwide.[9, 10] Previous studies[11, 12] have shown that patients with  
42 COPD are at increased risk for the development of lung cancer, and lung  
43 cancer is an important cause of death in patients with COPD.[13] Patients  
44 with COPD are at increased risk for lung cancer because most of them  
45 have a history of smoking. Additionally, patients with COPD are of lower  
46 socioeconomic status compared to the general population, and  
47 socioeconomic status may affect quality of life, including environmental  
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4 exposure to indoor and outdoor air pollution; these factors may influence  
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6 the development of lung cancer.

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8 Chronic inflammation after extracellular stimulation, such as tobacco  
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10 smoking and occupational and environmental inhalants, play a key role in  
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12 COPD and lung cancer. Thus, shared risk factors and inflammatory  
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14 pathways lead to the similar pathologic mechanisms of COPD and lung  
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16 cancer.[14]  
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### 20 21 **Liver cancer and COPD**

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23 Alpha1-antitrypsin deficiency is one of the most common inherited  
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25 disorders among white persons and predisposes individuals to COPD,  
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27 cirrhosis, and hepatomas.[15, 16] Alpha1-antitrypsin deficiency is not an  
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29 important cause of childhood liver diseases in Southeast Asian  
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31 populations[17] and is also rare in Taiwan. Liver cancer is one of the  
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33 most common tumour types in Taiwan because Taiwan has a high  
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35 prevalence of virus hepatitis, with approximately 20% of the general  
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37 population suffering from chronic hepatitis B virus infection and 4.4% of  
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39 the population from chronic hepatitis C virus infection.[18]  
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### 45 46 **Colorectal cancer and COPD**

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48 Colorectal cancer is one of the most common cancers in patients with  
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50 COPD.[19] Patients with COPD experienced sensations of dyspnoea in  
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52 their daily activities, and consequently tended to lead more sedentary  
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54 lifestyles; sedentary behavior may also increase the risk of colorectal  
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56 cancer. A nationwide population-based observational study investigated  
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4 the influence of COPD on intensive care unit admissions, medication  
5 treatments, and mortality following colorectal cancer surgery.[20] The  
6 authors identified 7.9% of colorectal cancer surgery patients as having a  
7 COPD diagnosis, and in this population, more complications were noted  
8 after surgery, including higher ICU admission rates, more frequent need  
9 for mechanical ventilation, higher rates of requiring reoperation, and  
10 more frequent inotropes/vasopressors. The thirty-day mortality after  
11 surgery was 13.0% in patients with colorectal cancer and COPD and  
12 5.3% in patients with colorectal cancer without COPD.  
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16 A study[21] demonstrated that COPD is one of the most common  
17 comorbid conditions in patients with colon cancer. The receipt of  
18 adjuvant therapy was related to COPD (55.2% vs 61.5% of patients with  
19 vs without COPD, respectively; OR, 0.83; 95% CI, 0.70–0.99), but  
20 patients with COPD and colon cancer had survival benefits after receipt  
21 of adjuvant therapy. Although COPD appeared to be a barrier to  
22 chemotherapy, chemotherapy can provide a survival benefit to patients  
23 who have colon cancer with COPD. Many colorectal cancers can be  
24 prevented through regular screening, and screening is also crucial in  
25 patients with COPD.  
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### 47 **Prostate cancer and COPD**

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49 Dysfunction in the hypothalamic–pituitary–gonadal axis, such as  
50 hypogonadotropic hypogonadism, has been noted in patients with  
51 COPD.[22, 23] The correlation between serum levels of testosterone and  
52 risk of prostate cancer is still controversial.[24, 25] One recent study  
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4 found that patients with COPD had a significant reduction in total and  
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6 free testosterone levels compared to controls.[26] The relationship  
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8 between testosterone level and prostate cancer in patients with COPD  
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10 needs further investigation. In our study, more than 80% of prostate  
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12 cancers were diagnosed in men who were 60 years of age or older. A  
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14 prostate-specific antigen-based screening test for prostate cancer may be  
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16 warranted in the elderly male population with COPD.  
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### 20 21 **Aerodigestive cancer and COPD**

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23 It is widely accepted that smoking is a risk factor for oropharyngeal  
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25 cancer, oesophageal cancer, and COPD. In our study, development of  
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27 cancers of the upper aerodigestive tract, including oropharyngeal and  
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29 oesophageal cancers, were also common in patients with COPD. A cohort  
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31 study among 17,774 men showed a positive association between smoking  
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33 and subsequent cancers of the upper aerodigestive tract (relative risk, 2.02;  
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35 95% CI, 1.01 to 4.06) with evidence of dose-response effects. Regular  
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37 smoking will increase the risk of COPD and aerodigestive tract and lung  
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39 cancers.[27] In addition to the same risk factor of smoking, the higher  
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41 risk of aerodigestive cancers in COPD patients can be partially explained  
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43 by socioeconomic status. A previous study showed that the risk of  
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45 aerodigestive cancers cannot be entirely explained by smoking, alcohol  
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47 consumption, and diet. Socioeconomic status was also a risk factor for  
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49 upper aerodigestive tract cancers.[28] There is growing recognition of the  
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51 importance of systematic examination of the oral cavity, oropharynx, and  
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53 neck, which can detect pre-cancers and cancers at an early and curable  
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4 stage in patients with COPD with a history of smoking.

### 5 **Cancer types in patients with COPD**

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8 Our study showed a positive association between COPD and the  
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10 subsequent development of cancer. The adjusted HR of developing cancer  
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12 in patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients  
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14 without COPD after adjusting for age, sex, and comorbidities. In a  
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16 previous study of the incidence of cancer, smoking increased the risk of  
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18 cancer of the oropharynx, upper aerodigestive tract, and lung.[27] From  
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20 our analysis, in addition to the cancers mentioned above, common cancer  
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22 types diagnosed with high frequency in patients with COPD included  
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24 liver, colon, and breast cancers.  
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28 A population-based study[29] revealed that 12% of all cancer patients  
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30 had COPD at the time of cancer diagnosis, with approximately 15% of  
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32 those patients over the age of 65. In addition to lung cancer, there was no  
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34 difference in the stage at diagnosis between cancer patients with or  
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36 without COPD. After using a multivariate Cox-regression model, the  
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38 survival rate was poor in patients with COPD, especially for elderly  
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40 patients with colon, rectum, larynx, prostate, or urinary bladder cancer.  
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44 Another study conducted in Taiwan also used the NHIRD, but the  
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46 researchers presented the risk of cancer in COPD using a standardized  
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48 incidence ratio. From 1995 to 2008, they enrolled 50,875 COPD patients  
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50 over 20 years of age and found that head and neck, oesophageal, lung and  
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52 mediastinal, breast, and prostate cancer were higher in patients with  
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54 COPD compared to the general population. In our study, we further  
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56 analysed prescription patterns, including prescriptions of bronchodilators  
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4 and steroids, in all patients with COPD from January 1, 2000 to  
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6 December 31, 2011, utilizing stricter inclusion criteria of patients over 40  
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8 years old who had attended at least three ambulatory medical visits for  
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10 COPD. In our study, we analysed the comorbidities of patients with and  
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12 without COPD and the hazard ratio of developing cancer in relation to the  
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14 baseline characteristics, which were not performed in the Chiang et al.  
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16 study. We also found that the risk of developing cancer was higher when  
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18 more bronchodilators were used. If patients with COPD use more than  
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20 two bronchodilators, representing COPD severity, the disease severity of  
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22 COPD may be associated with increased cancer risk. In summary, in  
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24 Chiang's study, the researchers included patient over 20 years of age,  
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26 while we enrolled patients aged over 40 years. The COPD patients in our  
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28 study were treated with COPD medications, and the non-COPD groups  
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30 were not treated with any COPD medications. In Chiang's study, they did  
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32 not survey COPD medications. Our study participants were exactly  
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34 matched by age and gender, and their comorbidities were analysed using  
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36 the Cox model. In Chiang's study, they used SIR to analyse the risk of  
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38 cancer. SIR cannot adjust for comorbidities or medications.  
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43 Kornum et al.[30] used the Danish National Registry of Patients and  
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45 their nationwide cancer registry databases to show the incidence of  
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47 various cancers in 236,494 patients with COPD from 1980 to 2008. They  
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49 included patients aged 40 years or older with COPD. Patients were  
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51 enrolled after a first-time hospitalization, outpatient clinic visit or a visit  
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53 to an emergency department with a diagnosis of COPD from ICD-8 or  
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55 IC-10 codes. The researchers focused on tobacco-related and  
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3 alcohol-related cancers, but they did not evaluate comorbidities and  
4 medications in patients with COPD. They found that lung, aerodigestive  
5 and liver cancers were increased in patients with COPD.  
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## 10 11 12 **Limitations**

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14 One major limitation was that some of the data, including histories of  
15 cigarette smoking, pulmonary function, degree of dyspnoea, COPD  
16 severity, and cancer staging, were not available from the claims database.  
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18 We used the database to demonstrate that COPD was significantly  
19 associated with a high risk of cancer, regardless of COPD severity. As a  
20 representation of COPD severity, we also divided the COPD population  
21 into 3 groups according to the number of medications they used to treat  
22 COPD. After the stratification, we found that patients who used more  
23 COPD medications were at a higher risk of developing cancer. Other  
24 limitations should be acknowledged, including that the data were based  
25 on insurance records that lacked consideration of other factors associated  
26 with COPD and cancer, such as lifestyle choices, physical activity, and  
27 socioeconomic status, which may have led to possible errors. The  
28 limitations of the analysis based on the database include an inability to  
29 truly characterize the patients and controls.  
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47 The study was a nationwide cohort study; we believe that the large  
48 number of participants, the comprehensive enrolment of patients with  
49 COPD, and the long-term follow-up ensured that the data are normally  
50 distributed and that the results are significant.  
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## 55 56 **Conclusion**

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4 In addition to lung cancer, patients with COPD have a higher risk of  
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6 developing other types of cancer, and physicians should closely monitor  
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8 and follow up with these patients.  
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14 **Contribution statement:** Chung-Han Ho: acquisition of data, analysis  
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16 and interpretation of data; Yi-Chen Chen: acquisition and analysis of data;  
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18 Jhi-Joung Wang: contributions to conception and design; Kuang-Ming  
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20 Liao: drafting the article and final approval of the version to be published.  
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24

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27 agency in the public, commercial, or not-for-profit sectors.  
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30 **Data sharing statement:** No additional data are available.  
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### Figure Legends

Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

Table 1 Demographic characteristics and comorbidities of patients with/without COPD

	COPD, n(%) (N=13,289)	Non-COPD, n(%) (N=26,578)	P-value
Sex			
Male	7148(53.8)	14296(53.8)	1.00
Female	6141(46.2)	12282(46.2)	
Age(years)			
40-49	3951(29.7)	7906(29.8)	1.00
50-59	4994(37.6)	9983(37.6)	
60-69	1980(14.9)	3961(14.9)	
≥70	2364(17.8)	4728(17.8)	
Mean±SD	57.9±13.5	57.9±13.5	1.00
Cancer	973(7.3)	708(2.7)	<0.01
Time to cancer (years)			
Mean±SD	3.9±3.2	5.0±3.2	<0.01
Comorbidity			
Cardiovascular disease	473(3.6)	36(0.1)	<0.01
Chronic kidney disease	227(1.7)	36(0.1)	<0.01
Liver disease	309(2.3)	70(0.3)	<0.01
Diabetes	797(6.0)	155(0.6)	<0.01
Hyperlipidaemia	191(1.4)	38(0.1)	<0.01
COPD medications			
1	7452(56.1)		-
2	3660(27.5)		
≥ 3	2177(16.4)		

SD=standard deviation

Table 2. Hazard ratio of developing cancer in relation to baseline characteristics of the study subjects

	Crude HR <sup>a</sup> (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> (95% CI <sup>a</sup> )	P-value
Patients				
COPD	2.9(2.7-3.2)	<0.01	2.8(2.6-3.1)	<0.01
Non-COPD	1.0(ref.)		1.0(ref.)	
Sex				
Male	1.3(1.2-1.4)	<0.01	1.3(1.2-1.4)	<0.01
Female	1.0(ref.)		1.0(ref.)	
Age(years)				
40-49	1.0(ref.)		1.0(ref.)	
50-59	1.7(1.5-2.0)	<0.01	1.7(1.5-1.9)	<0.01
60-69	2.4(2.1-2.8)	<0.01	2.4(2.1-2.8)	<0.01
>70	1.5(1.3-1.8)	<0.01	1.6(1.4-1.9)	<0.01
Comorbidity				
Cardiovascular disease	1.8(1.2-2.5)	<0.01	0.8(0.6-1.2)	0.31
Chronic kidney disease	2.2(1.4-3.4)	<0.01	1.0(0.7-1.6)	0.84
Liver disease	4.1(3.1-5.3)	<0.01	2.3(1.8-3.1)	<0.01
Diabetes	2.7(2.2-3.4)	<0.01	1.4(1.1-1.8)	<0.01
Hyperlipidaemia	2.4(1.6-3.9)	<0.01	1.1(0.7-1.8)	0.69

<sup>a</sup> HR=hazard ratio; CI= confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustment for age, sex, and comorbidities.

Table 3. Hazard ratio of developing cancer in relation to baseline characteristics and COPD medications of the study subjects

	AHR <sup>b</sup> of cancer among all study subjects (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> of cancer for patients with COPD only (95% CI <sup>a</sup> )	P-value
Patients				
Non-COPD	1.0(ref.)		-	
COPD with only 1 medication	2.6(2.3-3.0)	<0.01	1.0(ref.)	
COPD with 2 medication	3.0(2.6-3.4)	<0.01	1.1(1.0-1.3)	0.16
COPD with ≥3 medication	3.3(2.8-3.9)	<0.01	1.2(1.0-1.5)	0.02
Sex				
Male	1.3(1.2-1.4)	<0.01	1.6(1.4-1.8)	<0.01
Female	1.0(ref.)		1.0(ref.)	
Age(years)				
40-49	1.0(ref.)		1.0(ref.)	
50-59	1.7(1.5-1.9)	<0.01	1.8(1.5-2.2)	<0.01
60-69	2.4(2.1-2.8)	<0.01	2.5(2.1-3.1)	<0.01
>70	1.6(1.4-1.9)	<0.01	2.2(1.8-2.7)	<0.01
Comorbidity				
Cardiovascular disease	0.8(0.6-1.2)	0.27	0.8(0.5-1.1)	0.15
Chronic kidney disease	1.1(0.7-1.7)	0.82	1.1(0.7-1.7)	0.76
Liver disease	2.3(1.8-3.1)	<0.01	2.3(1.7-3.1)	<0.01
Diabetes	1.4(1.1-1.8)	<0.01	1.3(1.0-1.7)	0.02
Hyperlipidaemia	1.1(0.7-1.8)	0.68	1.1(0.7-1.8)	0.66

<sup>a</sup> CI=confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustments for age, sex, and comorbidities.

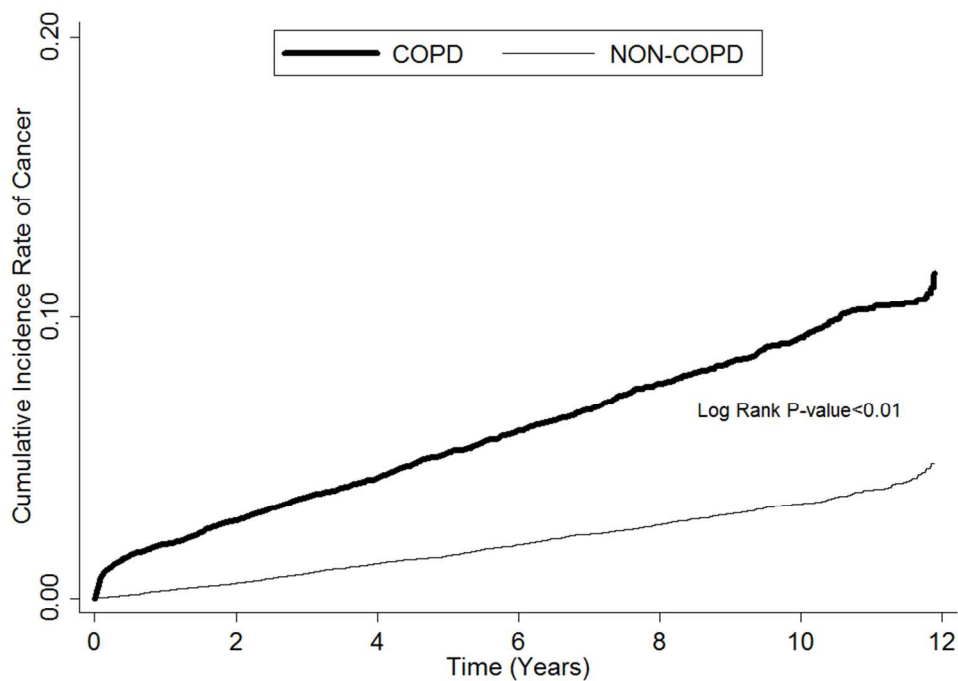


Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

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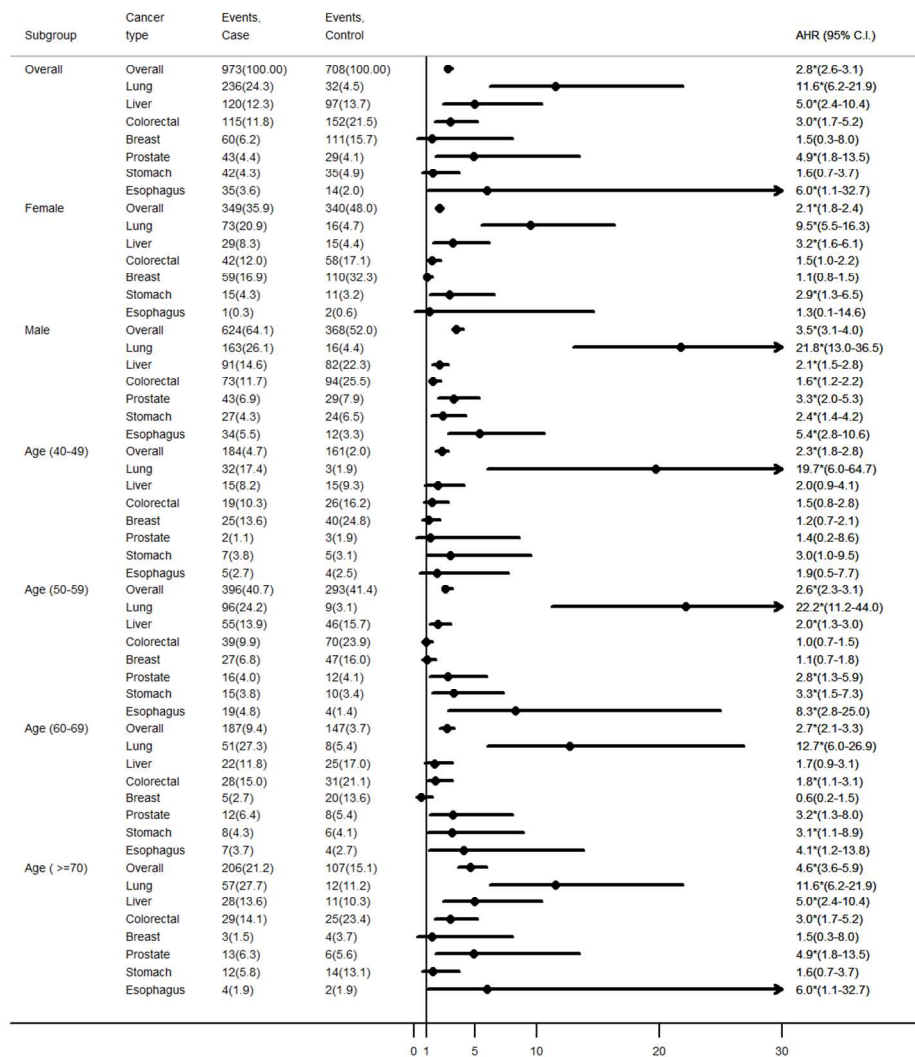


Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

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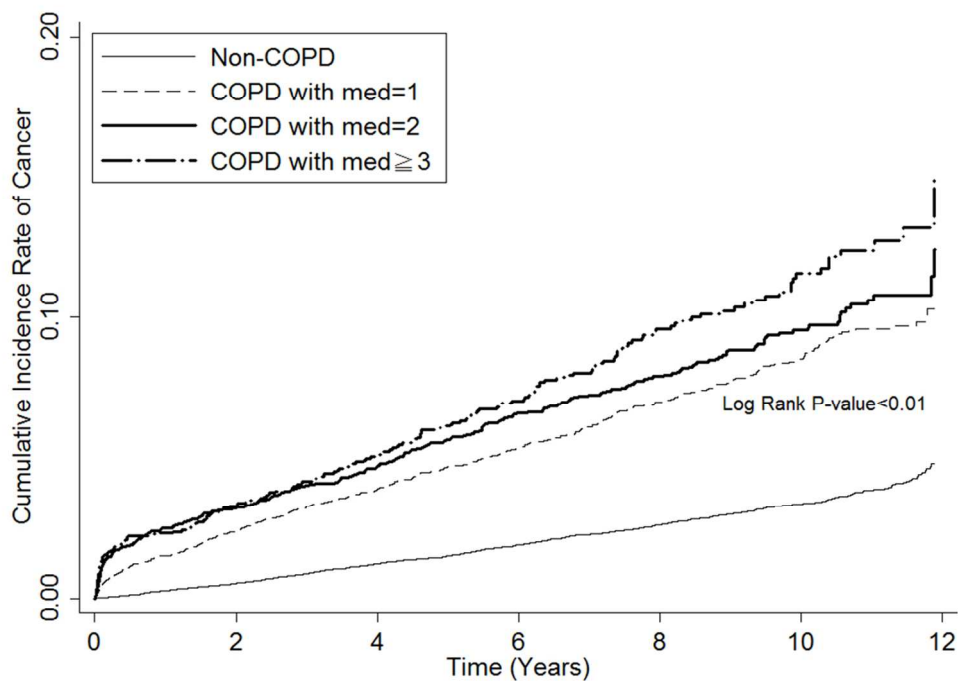


Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

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## STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
		(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
Participants	6	<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4,5
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	5
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Study size	10	Describe any efforts to address potential sources of bias	6
Quantitative variables	11	Explain how the study size was arrived at	5,6
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5,6
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7,8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(b) Report category boundaries when continuous variables were categorized	7,8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
<b>Other Information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## The Incidence and Relative Risk for Developing Cancer Among Patients with COPD: A Nationwide Cohort Study in Taiwan

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<b>Primary Subject Heading</b>:	Respiratory medicine
Secondary Subject Heading:	Oncology
Keywords:	Cancer, Chronic obstructive pulmonary disease, EPIDEMIOLOGY

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Manuscripts

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4 **The Incidence and Relative Risk for Developing Cancer**  
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7 **Among Patients with COPD: A Nationwide Cohort Study in**  
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10 **Taiwan**

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51 Abbreviations: COPD = chronic obstructive pulmonary disease; NHI = National  
52 Health Insurance; NHIRD = National Health Insurance Research Database; HR =  
53 hazard ratio; CI = confidence interval; OR = odds ratio.  
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56 Disclosure: All authors report no disclosures relevant to the manuscript.  
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## Abstract

**Objectives:** This observational study aimed to examine the incidence of malignant diseases, including specific cancer types, after the diagnosis of chronic obstructive pulmonary disease (COPD) in Taiwanese patients.

**Setting:** Taiwan's National Health Insurance Research Database.

**Participants:** The definition of a patient with COPD was a patient with a discharge diagnosis of COPD or at least three ambulatory visits for COPD. The index date was the date of the first COPD diagnosis. Patients with a history of malignancy disorders before the index date were excluded. After matching age and gender, 13,289 patients with COPD and 26,578 control subjects without COPD were retrieved and analyzed. They were followed from the index date to malignancy diagnosis, death, or the end of study follow-up (December 31, 2011), whichever came first.

**Primary outcome measures:** Patients were diagnosed with cancer [n=1681, 4.2%; 973 (7.3%) for COPD patients and 728 (2.7%) for non-COPD patients]. The risk of seven major cancer types, including lung, liver, colorectal, breast, prostate, stomach, and esophagus, between COPD patients and non-COPD patients was also estimated.

**Results:** The mean age of all study subjects was 57.9±13.5 years. The average length of follow-up to cancer incidence was 3.9 years for COPD patients and 5.0 years for patients without COPD (p<0.01). Patients with COPD were diagnosed with cancer (n=973, 73%) at a significantly higher rate than patients without COPD (n=708, 2.7%) (p<0.01). The hazard ratio for developing cancer in patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients without COPD after adjusting for age, sex, and comorbidities. The most common cancers in patients with COPD included lung, liver, colorectal, breast, prostate, and stomach cancers.

**Conclusions:** The risk of developing cancer is higher in patients with COPD compared with patients without COPD. Cancer screening is warranted in patients with

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### 8 **Strengths and limitations of this study**

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- 10 1. We analysed the risk of different cancer types in patients with COPD and stratified  
11 them by disease severity according to the number of prescription drugs.  
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  - 13 2. The patients with COPD in our study were treated with COPD medications and  
14 were over 40 years old. Our study groups were matched by age and gender, and  
15 the data were analysed using the Cox model, including patient comorbidities. Our  
16 method differed from the standardized incidence ratio, which cannot adjust for  
17 comorbidities or medications.  
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  - 19 3. This study was a nationwide cohort study with a large number of participants,  
20 comprehensive enrolment of patients with COPD, and long-term follow up.  
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  - 22 4. The limitations included lack of COPD severity information and cancer staging  
23 from the claims database.  
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  - 25 5. The data lacked consideration of other factors associated with COPD and cancer,  
26 such as lifestyle choices, physical activity, and socioeconomic status.  
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38 **Keywords:** Cancer; chronic obstructive pulmonary disease  
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## Introduction:

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible, and the disease is usually progressive and associated with lung inflammatory responses to noxious particles or gases.[1] COPD was the sixth most common cause of death worldwide in 1990, and it was predicted to become the third most common cause by 2020.[2] Cigarette smoking is the most common cause of COPD, and smoking is a risk factor for lung cancer. Lung cancer risk increases with decreasing lung function in patients with COPD.[3] The systemic effects of smoking and chronic systemic inflammation responses in patients with COPD contribute to the development of respiratory symptoms, functional impairment, and chronic comorbidities and include extra-pulmonary cancers.[4] A previous study demonstrated that COPD was associated with an increased risk of both lung cancer mortality and extra-pulmonary cancer mortality.[5] In other cohort studies,[4-8] patients with COPD had increased mortality and risk of extra-pulmonary cancers. However, previous studies have been limited by few participants or studying only populations at local hospitals, and none of the other studies mention specific types of extra-pulmonary cancers. The aim of this study was to use a nationwide cohort database to examine the incidence of malignant diseases, including specific cancer types, in Taiwanese patients after diagnosis with COPD compared with Taiwanese patients without COPD.

## Materials and Methods:

### *Ethics statement*

This study was conducted using an unidentifiable claims database provided by the National Health Insurance (NHI), and the principal investigator was requested to sign an agreement regarding compliance with the Computer-Processed Personal Data Protection Act during the proposal application. In addition, the policy of our institutional review board (IRB) is consistent with the principles of the Declaration of Helsinki. This study was approved by the IRB of the Chi Mei Medical Center (IRB no. 10405-E03).

### *Source of data*

Taiwan launched a single-payer NHI program in 1995. The National Health Insurance Research Database (NHIRD), a medical claims database, was established and released for research purposes. The NHIRD contains all inpatient and outpatient claims data in Taiwan, including patients' demographic characteristics, dates of clinical visits, disease diagnoses, prescription medications, and expenditure amounts. More than 99% of the total population of Taiwan was enrolled in the NHI Program. In this study, we analysed the claim data of one million beneficiaries (from January 1, 2000 to December 31, 2011) randomly sampled from all of the beneficiaries registered in 2000.

### *Study groups*

In the present study, the definition of a patient with COPD was a patient with a discharge diagnosis of COPD (ICD-9-CM codes: 490-492, 496) or at least three ambulatory visits for COPD who was also

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4 prescribed COPD medications, including short acting  $\beta$ 2 agonists  
5 (SABA), long-acting  $\beta$ 2 agonists (LABA), theophylline, inhaled  
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7 short-acting muscarinic antagonists (SAMA), long-acting muscarinic  
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9 antagonists (LAMA), combination inhaled corticosteroid/long-acting  $\beta$ 2  
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11 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC).  
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13 Included patients were those over 40 years of age who received a  
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15 diagnosis of COPD between January 1, 2000 and December 31, 2010.  
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17 The index date was the date of the first COPD diagnosis. Patients with a  
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19 history of malignancy disorders (ICD-9-CM codes 140 to 208) before the  
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21 index date were excluded. During the study period, more than one  
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23 readmission event may have occurred for the same patient; only the data  
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25 from the first-time hospitalization record for COPD were analysed to  
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27 ensure the independence of observations. In total, 13,289 patients with  
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29 COPD were retrieved and analysed.  
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34 The control subjects were selected from the remaining patients without  
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36 COPD and with no history of malignancy before the index date. Patients  
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38 who were treated with any of the above COPD medications were also  
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40 excluded. Considering that cancer was a rare event and a stratified  
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42 analysis for seven cancer types was used in our study, patients with  
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44 COPD were matched 1:2 for age and gender to the control subjects  
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46 without COPD. In total, 26,578 patients without COPD or malignancy  
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48 were selected as controls. Case and control subjects were followed from  
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50 the index date to malignancy diagnosis, death, or the end of study  
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52 follow-up (December 31, 2011), whichever came first.  
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### ***Definition of malignancy cases***

The Registry of Catastrophic Illness Database was used in cancer diagnosis. When a patient is diagnosed by a physician as having a malignancy, under Ministry of Health and Welfare guidelines, the patient can submit related information and apply for a catastrophic illness certificate. The application is formally reviewed by more than two physicians. Patients with in situ malignancies were excluded from this study because patients with in situ malignancies do not qualify for a catastrophic illness certificate.

### ***Comorbidities and medication measures***

Baseline comorbidities were assessed for one year before the index date. They included chronic kidney disease, liver disease, diabetes, and hyperlipidaemia and were recognized by the ICD-9-CM codes used to define each condition. COPD medication use on the index date was recorded. We examined the use of oral steroids, SABA, LABA, theophylline, ICS, SAMA, LAMA, ICS/LABA, MTX, and AC. For estimating the effect of the number of COPD medications, COPD patients in our study were divided into three groups: only one type of COPD medication, two types of COPD medication, and more than two types of COPD medication.

### ***Statistical analysis***

We described the demographic characteristics of the patients, including age, gender, Charlson comorbidity index, comorbidities, and COPD

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4 medications. Continuous variables are presented as the means with  
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6 standard deviations (SD), and discrete variables are presented as counts  
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8 and percentages. Chi-square test was used for comparing categorical  
9  
10 variables, and the differences among continuous variables were compared  
11  
12 using Student's t test. The proportion of cancer patients was plotted by  
13  
14 Kaplan-Meier curves with log-rank test for comparing the differences  
15  
16 between COPD and non-COPD patients. The relative risk of cancer was  
17  
18 estimated by Cox proportional regression analysis, which was adjusted  
19  
20 for potential confounding variables, such as age, sex, and comorbidities.  
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22 The statistical significance was inferred at a two-sided p value of <0.05.  
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24 All of the statistical analyses were performed using the Statistical  
25  
26 Analysis Software (SAS) System, version 9.4 (SAS Institute Inc., Cary,  
27  
28 NC, USA). Kaplan-Meier curves were plotted using Stata 12 (Stata Corp.,  
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30 College Station, TX, USA).  
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### 39 **Result:**

40 The characteristics and comorbidities of the study subjects are shown  
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42 in Table 1. Overall, 13,289 patients with COPD enrolled in the study. The  
43  
44 mean age $\pm$ SD of the COPD patients was 57.9 $\pm$ 13.5 years. A ten-year age  
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46 group distribution showed that 29.7% were 49 years of age or younger,  
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48 37.6% were 50-59 years, 14.9% were 60-69 years, and 17.8% were 70  
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50 years of age or older. The average length of follow-up was 3.9 years from  
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52 COPD diagnosis to patients being diagnosed with any type of cancers  
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54 compared with 5.0 years in the control groups (p<0.01). Patients with  
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56 COPD were diagnosed with cancer (n=973, 73%) at significantly higher  
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3 rates than patients without COPD (n=708, 2.7%) (p<0.01). The patients  
4 with COPD had a higher prevalence of comorbidities than the control  
5 group (p<0.01), including cardiovascular disease, chronic kidney disease,  
6 liver disease, diabetes, and dyslipidaemia.  
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11  
12 Figure 1 shows the cumulative incidence rate of any type of cancer in  
13 patients with or without COPD from the index date until the first  
14 occurrence of the cancer using Kaplan-Meier methods. The patients with  
15 COPD had higher cancer incidence rates compared with patients without  
16 COPD (log-rank test: p<0.01). Table 2 shows that the adjusted HR of  
17 developing cancer among patients with COPD was 2.8 (95% CI: 2.6-3.1)  
18 compared to patients without COPD after adjusting for age, sex, and  
19 comorbidities. For comparing the risk of cancer among each of the seven  
20 cancer types between COPD and non-COPD patients, the adjusted hazard  
21 ratios for each cancer type are reported in Figure 2. Patients with COPD  
22 had significantly higher risks of lung (AHR: 11.6; 95% C.I.: 6.2-21.9),  
23 liver (AHR: 5.0; 95% C.I.: 2.4-10.4), colorectal (AHR: 3.0; 95% C.I.:  
24 1.7-5.2), prostate (AHR: 4.9; 95% C.I.: 1.8-13.5), and oesophageal (AHR:  
25 6.0; 95% C.I.: 1.1-32.7) cancer. Moreover, the stratified analysis of the  
26 cancer risk between COPD and non-COPD patients by age group and sex  
27 for any type of cancer and each of the seven cancer types is also  
28 presented (Figure 2).  
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49 Patients with COPD were divided into three groups according to the  
50 number of medications used to treat COPD, and Figure 3 shows the  
51 cumulative incidence rates of any type of cancer in patients with or  
52 without COPD. Patients had a higher risk of developing cancer when  
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more bronchodilator medications were used.

Table 3 shows the adjusted HR of developing cancer in patients with COPD who were taking multiple COPD medications compared with non-COPD patients or COPD patients who were treated with only one COPD medication after adjusting for age, sex, and comorbidities. COPD patients who were treated with COPD medications had a 2.6-fold (95% C.I.: 2.3-3.0), 3.0-fold (95% C.I.: 2.6-3.4), and 3.3-fold (95% C.I.: 2.8-3.9) risk of any types of cancer for one, two, and more than two medication treatments, respectively, compared with patients without COPD. The AHR of developing cancer among patients with COPD who used more than two types of COPD medication was 1.2 (95% C.I.: 1.0-1.5) compared to patients with COPD who only used one type of medication. In addition, the adjusted HR of developing cancer was 1.6 (95% C.I.: 1.4-1.8) in male COPD patients compared to female COPD patients after adjusting for age and comorbidities. Being elderly was associated with a higher risk of developing cancer [50-59, AHR: 1.8 (95% C.I.: 1.5-2.2); 60-69, AHR: 2.5 (95% C.I.: 2.1-3.1); >70, AHR: 2.2 (95% C.I.: 1.8-2.7)]. Liver disease and diabetes were associated with a higher risk of developing cancer after adjusting for age, sex, and comorbidities [liver disease, AHR: 2.3 (95% C.I.: 1.7-3.1); diabetes, AHR: 1.3 (95% C.I.: 1.0-1.7)].

## Discussion

### Cancer type in patients with COPD

This is the first study to show the common types of cancer among

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4 patients with COPD. The five most common cancers after COPD  
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6 diagnosis included: lung cancer, liver cancer, colorectal cancer, prostate  
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8 cancer, and oesophageal cancer in male patients and lung cancer, breast  
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10 cancer, colorectal cancer, liver cancer, and stomach cancer in female  
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12 patients. Patients with COPD had a higher risk of developing cancer and  
13  
14 developed cancer within a shorter period of time compared with the  
15  
16 non-COPD population. Patients with COPD had a high prevalence of  
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18 comorbidities compared to the non-COPD population, including chronic  
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20 kidney disease, liver disease, diabetes, and dyslipidaemia. Patients with  
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22 COPD had an elevated risk of developing cancer when they used more  
23  
24 types of COPD medications compared with the non-COPD population. In  
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26 patients with COPD, the risk of developing cancer was significant when  
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28 they used more than two types of COPD medications compared to the  
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30 COPD patients who only used one type of COPD medication.  
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### 36 **Lung cancer and COPD**

37  
38 Both COPD and lung cancer have high morbidity and mortality rates  
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40 worldwide.[9, 10] Previous studies[11, 12] have shown that patients with  
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42 COPD are at increased risk for the development of lung cancer, and lung  
43  
44 cancer is an important cause of death in patients with COPD.[13] Patients  
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46 with COPD are at increased risk for lung cancer because most of them  
47  
48 have a history of smoking. Additionally, patients with COPD are of lower  
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50 socioeconomic status compared to the general population, and  
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52 socioeconomic status may affect quality of life, including environmental  
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54 exposure to indoor and outdoor air pollution; these factors may influence  
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4 the development of lung cancer.

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6 Chronic inflammation after extracellular stimulation, such as tobacco  
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8 smoking and occupational and environmental inhalants, play a key role in  
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10 COPD and lung cancer. Thus, shared risk factors and inflammatory  
11  
12 pathways lead to the similar pathologic mechanisms of COPD and lung  
13  
14 cancer.[14]  
15

### 16 17 18 19 **Liver cancer and COPD**

20  
21 Alpha1-antitrypsin deficiency is one of the most common inherited  
22  
23 disorders among white persons and predisposes individuals to COPD,  
24  
25 cirrhosis, and hepatomas.[15, 16] Alpha1-antitrypsin deficiency is not an  
26  
27 important cause of childhood liver diseases in Southeast Asian  
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29 populations[17] and is also rare in Taiwan. Liver cancer is one of the  
30  
31 most common tumour types in Taiwan because Taiwan has a high  
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33 prevalence of virus hepatitis, with approximately 20% of the general  
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35 population suffering from chronic hepatitis B virus infection and 4.4% of  
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37 the population from chronic hepatitis C virus infection.[18]  
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### 42 43 44 **Colorectal cancer and COPD**

45  
46 Colorectal cancer is one of the most common cancers in patients with  
47  
48 COPD.[19] Patients with COPD experienced sensations of dyspnoea in  
49  
50 their daily activities, and consequently tended to lead more sedentary  
51  
52 lifestyles; sedentary behavior may also increase the risk of colorectal  
53  
54 cancer. A nationwide population-based observational study investigated  
55  
56 the influence of COPD on intensive care unit admissions, medication  
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4 treatments, and mortality following colorectal cancer surgery.[20] The  
5  
6 authors identified 7.9% of colorectal cancer surgery patients as having a  
7  
8 COPD diagnosis, and in this population, more complications were noted  
9  
10 after surgery, including higher ICU admission rates, more frequent need  
11  
12 for mechanical ventilation, higher rates of requiring reoperation, and  
13  
14 more frequent inotropes/vasopressors. The thirty-day mortality after  
15  
16 surgery was 13.0% in patients with colorectal cancer and COPD and  
17  
18 5.3% in patients with colorectal cancer without COPD.  
19

20  
21 A study[21] demonstrated that COPD is one of the most common  
22  
23 comorbid conditions in patients with colon cancer. The receipt of  
24  
25 adjuvant therapy was related to COPD (55.2% vs 61.5% of patients with  
26  
27 vs without COPD, respectively; OR, 0.83; 95% CI, 0.70–0.99), but  
28  
29 patients with COPD and colon cancer had survival benefits after receipt  
30  
31 of adjuvant therapy. Although COPD appeared to be a barrier to  
32  
33 chemotherapy, chemotherapy can provide a survival benefit to patients  
34  
35 who have colon cancer with COPD. Many colorectal cancers can be  
36  
37 prevented through regular screening, and screening is also crucial in  
38  
39 patients with COPD.  
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#### 45 **Prostate cancer and COPD**

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47 Dysfunction in the hypothalamic–pituitary–gonadal axis, such as  
48  
49 hypogonadotropic hypogonadism, has been noted in patients with  
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51 COPD.[22, 23] The correlation between serum levels of testosterone and  
52  
53 risk of prostate cancer is still controversial.[24, 25] One recent study  
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55 found that patients with COPD had a significant reduction in total and  
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4 free testosterone levels compared to controls.[26] The relationship  
5  
6 between testosterone level and prostate cancer in patients with COPD  
7  
8 needs further investigation. In our study, more than 80% of prostate  
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10 cancers were diagnosed in men who were 60 years of age or older. A  
11  
12 prostate-specific antigen-based screening test for prostate cancer may be  
13  
14 warranted in the elderly male population with COPD.  
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### 17 18 19 **Aerodigestive cancer and COPD**

20  
21 It is widely accepted that smoking is a risk factor for oropharyngeal  
22  
23 cancer, oesophageal cancer, and COPD. In our study, development of  
24  
25 cancers of the upper aerodigestive tract, including oropharyngeal and  
26  
27 oesophageal cancers, were also common in patients with COPD. A cohort  
28  
29 study among 17,774 men showed a positive association between smoking  
30  
31 and subsequent cancers of the upper aerodigestive tract (relative risk, 2.02;  
32  
33 95% CI, 1.01 to 4.06) with evidence of dose-response effects. Regular  
34  
35 smoking will increase the risk of COPD and aerodigestive tract and lung  
36  
37 cancers.[27] In addition to the same risk factor of smoking, the higher  
38  
39 risk of aerodigestive cancers in COPD patients can be partially explained  
40  
41 by socioeconomic status. A previous study showed that the risk of  
42  
43 aerodigestive cancers cannot be entirely explained by smoking, alcohol  
44  
45 consumption, and diet. Socioeconomic status was also a risk factor for  
46  
47 upper aerodigestive tract cancers.[28] There is growing recognition of the  
48  
49 importance of systematic examination of the oral cavity, oropharynx, and  
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51 neck, which can detect pre-cancers and cancers at an early and curable  
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53 stage in patients with COPD with a history of smoking.  
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## Cancer types in patients with COPD

Our study showed a positive association between COPD and the subsequent development of cancer. The adjusted HR of developing cancer in patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients without COPD after adjusting for age, sex, and comorbidities. In a previous study of the incidence of cancer, smoking increased the risk of cancer of the oropharynx, upper aerodigestive tract, and lung.[27] From our analysis, in addition to the cancers mentioned above, common cancer types diagnosed with high frequency in patients with COPD included liver, colon, and breast cancers.

A population-based study[29] revealed that 12% of all cancer patients had COPD at the time of cancer diagnosis, with approximately 15% of those patients over the age of 65. In addition to lung cancer, there was no difference in the stage at diagnosis between cancer patients with or without COPD. After using a multivariate Cox-regression model, the survival rate was poor in patients with COPD, especially for elderly patients with colon, rectum, larynx, prostate, or urinary bladder cancer.

Another study conducted in Taiwan also used the NHIRD, but the researchers presented the risk of cancer in COPD using a standardized incidence ratio. From 1995 to 2008, they enrolled 50,875 COPD patients over 20 years of age and found that head and neck, oesophageal, lung and mediastinal, breast, and prostate cancer were higher in patients with COPD compared to the general population. In our study, we further analyzed the prescription pattern, including bronchodilators and steroid, in all patients with COPD from January 1, 2000 to December 31, 2011

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3 with stricter inclusion criteria which aged more than 40 years and visit at  
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5 least three ambulatory visits for COPD. In our study, we analyzed the  
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7 comorbidities in patients with and without COPD and hazard ratio of  
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9 developing cancer in relation to baseline characteristics which did not  
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11 performed in Chiang et al. study. We also found that the more  
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13 bronchodilators patients with COPD used, the more risk of developing  
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15 cancer. If patients with COPD used more than 2 bronchodilators  
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17 representing COPD severity, the disease severity of COPD may be  
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19 associated with increasing cancer risk.  
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23 In summary, in Chiang's study, they included patient aged more than  
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25 20 years. We enrolled patient aged more than 40 years. The COPD  
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27 patients in our study were treated with COPD medications and  
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29 non-COPD groups did not treated with any COPD medications. In  
30  
31 Chiang's study, they did not survey the COPD medications. Our study  
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33 exactly match by age and gender with Cox model and analyzed the  
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35 comorbidities. In Chiang's study, they used SIR to analyze the risk of  
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37 cancer. SIR cannot adjust comorbidity and medications.  
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41 In figure 2, consistent with the results of Chiang's studies, patients with  
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43 COPD had a higher risk of lung, aerodigestive and prostate cancer. There  
44  
45 was difference in association between COPD and cancers in our study  
46  
47 compared to Chiang's study after adjusting for age and gender. In our  
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49 study, patients with COPD had a higher risk of liver and colorectal cancer  
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51 compared to patients without COPD. Although the risk of head and neck  
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53 cancer was higher in patients with COPD compared to general population  
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55 in Chiang's study, there was no significant difference risk in our study  
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3 after adjusting for age and gender. In addition to lung and aerodigestive  
4 cancer, we suggest that patients with COPD follow-up cancer screening  
5 may include liver and colorectal cancer.  
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10 Kornum et al.[30] used the Danish National Registry of Patients and  
11 their nationwide cancer registry databases to show the incidence of  
12 various cancers in 236,494 patients with COPD from 1980 to 2008. They  
13 included patients aged 40 years or older with COPD. Patients were  
14 enrolled after a first-time hospitalization, outpatient clinic visit or a visit  
15 to an emergency department with a diagnosis of COPD from ICD-8 or  
16 IC-10 codes. The researchers focused on tobacco-related and  
17 alcohol-related cancers, but they did not evaluate comorbidities and  
18 medications in patients with COPD. They found that lung, aerodigestive  
19 and liver cancers were increased in patients with COPD.  
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### 34 **Limitations**

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36 One major limitation was that some of the data, including histories of  
37 cigarette smoking, pulmonary function, degree of dyspnoea, COPD  
38 severity, and cancer staging, were not available from the claims database.  
39 We used the database to demonstrate that COPD was significantly  
40 associated with a high risk of cancer, regardless of COPD severity. As a  
41 representation of COPD severity, we also divided the COPD population  
42 into 3 groups according to the number of medications they used to treat  
43 COPD. After the stratification, we found that patients who used more  
44 COPD medications were at a higher risk of developing cancer. Other  
45 limitations should be acknowledged, including that the data were based  
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4 on insurance records that lacked consideration of other factors associated  
5 with COPD and cancer, such as lifestyle choices, physical activity, and  
6 socioeconomic status, which may have led to possible errors. The  
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8 limitations of the analysis based on the database include an inability to  
9  
10 truly characterize the patients and controls.  
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14 The study was a nationwide cohort study; we believe that the large  
15 number of participants, the comprehensive enrolment of patients with  
16 COPD, and the long-term follow-up ensured that the data are normally  
17 distributed and that the results are significant.  
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### 20 21 22 **Conclusion**

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24 In addition to lung cancer, patients with COPD have a higher risk of  
25 developing other types of cancer, and physicians should closely monitor  
26 and follow up with these patients.  
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36 **Contribution statement:** Chung-Han Ho: acquisition of data, analysis  
37 and interpretation of data; Yi-Chen Chen: acquisition and analysis of data;  
38  
39 Jhi-Joung Wang: contributions to conception and design; Kuang-Ming  
40 Liao: drafting the article and final approval of the version to be published.  
41  
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46

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48 agency in the public, commercial, or not-for-profit sectors.  
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51 **Data sharing statement:** No additional data are available.  
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### Figure Legends

Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

Table 1 Demographic characteristics and comorbidities of patients with/without COPD

	COPD, n(%) (N=13,289)	Non-COPD, n(%) (N=26,578)	P-value
Sex			
Male	7148(53.8)	14296(53.8)	1.00
Female	6141(46.2)	12282(46.2)	
Age(years)			
40-49	3951(29.7)	7906(29.8)	1.00
50-59	4994(37.6)	9983(37.6)	
60-69	1980(14.9)	3961(14.9)	
≥70	2364(17.8)	4728(17.8)	
Mean±SD	57.9±13.5	57.9±13.5	1.00
Cancer	973(7.3)	708(2.7)	<0.01
Time to cancer (years)			
Mean±SD	3.9±3.2	5.0±3.2	<0.01
Comorbidity			
Cardiovascular disease	473(3.6)	36(0.1)	<0.01
Chronic kidney disease	227(1.7)	36(0.1)	<0.01
Liver disease	309(2.3)	70(0.3)	<0.01
Diabetes	797(6.0)	155(0.6)	<0.01
Hyperlipidaemia	191(1.4)	38(0.1)	<0.01
COPD medications			
1	7452(56.1)		-
2	3660(27.5)		
≥ 3	2177(16.4)		

SD=standard deviation

Table 2. Hazard ratio of developing cancer in relation to baseline characteristics of the study subjects

	Crude HR <sup>a</sup> (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> (95% CI <sup>a</sup> )	P-value
Patients				
COPD	2.9(2.7-3.2)	<0.01	2.8(2.6-3.1)	<0.01
Non-COPD	1.0(ref.)		1.0(ref.)	
Sex				
Male	1.3(1.2-1.4)	<0.01	1.3(1.2-1.4)	<0.01
Female	1.0(ref.)		1.0(ref.)	
Age(years)				
40-49	1.0(ref.)		1.0(ref.)	
50-59	1.7(1.5-2.0)	<0.01	1.7(1.5-1.9)	<0.01
60-69	2.4(2.1-2.8)	<0.01	2.4(2.1-2.8)	<0.01
>70	1.5(1.3-1.8)	<0.01	1.6(1.4-1.9)	<0.01
Comorbidity				
Cardiovascular disease	1.8(1.2-2.5)	<0.01	0.8(0.6-1.2)	0.31
Chronic kidney disease	2.2(1.4-3.4)	<0.01	1.0(0.7-1.6)	0.84
Liver disease	4.1(3.1-5.3)	<0.01	2.3(1.8-3.1)	<0.01
Diabetes	2.7(2.2-3.4)	<0.01	1.4(1.1-1.8)	<0.01
Hyperlipidaemia	2.4(1.6-3.9)	<0.01	1.1(0.7-1.8)	0.69

<sup>a</sup> HR=hazard ratio; CI= confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustment for age, sex, and comorbidities.

Table 3. Hazard ratio of developing cancer in relation to baseline characteristics and COPD medications of the study subjects

	AHR <sup>b</sup> of cancer among all study subjects (95% CI <sup>a</sup> )	P-value	†AHR <sup>b</sup> of cancer for COPD patients alone (95% CI <sup>a</sup> )	P-value
Patients				
Non-COPD	1.0(ref.)		-	
COPD with only 1 medication	2.6(2.3-3.0)	<0.01	1.0(ref.)	
COPD with 2 medication	3.0(2.6-3.4)	<0.01	1.1(1.0-1.3)	0.16
COPD with ≥3 medication	3.3(2.8-3.9)	<0.01	1.2(1.0-1.5)	0.02
Sex				
Male	1.3(1.2-1.4)	<0.01	1.6(1.4-1.8)	<0.01
Female	1.0(ref.)		1.0(ref.)	
Age(years)				
40-49	1.0(ref.)		1.0(ref.)	
50-59	1.7(1.5-1.9)	<0.01	1.8(1.5-2.2)	<0.01
60-69	2.4(2.1-2.8)	<0.01	2.5(2.1-3.1)	<0.01
>70	1.6(1.4-1.9)	<0.01	2.2(1.8-2.7)	<0.01
Comorbidity				
Cardiovascular disease	0.8(0.6-1.2)	0.27	0.8(0.5-1.1)	0.15
Chronic kidney disease	1.1(0.7-1.7)	0.82	1.1(0.7-1.7)	0.76
Liver disease	2.3(1.8-3.1)	<0.01	2.3(1.7-3.1)	<0.01
Diabetes	1.4(1.1-1.8)	<0.01	1.3(1.0-1.7)	0.02
Hyperlipidaemia	1.1(0.7-1.8)	0.68	1.1(0.7-1.8)	0.66

<sup>a</sup> CI=confidence interval

<sup>b</sup> AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustments for age, sex, and comorbidities.



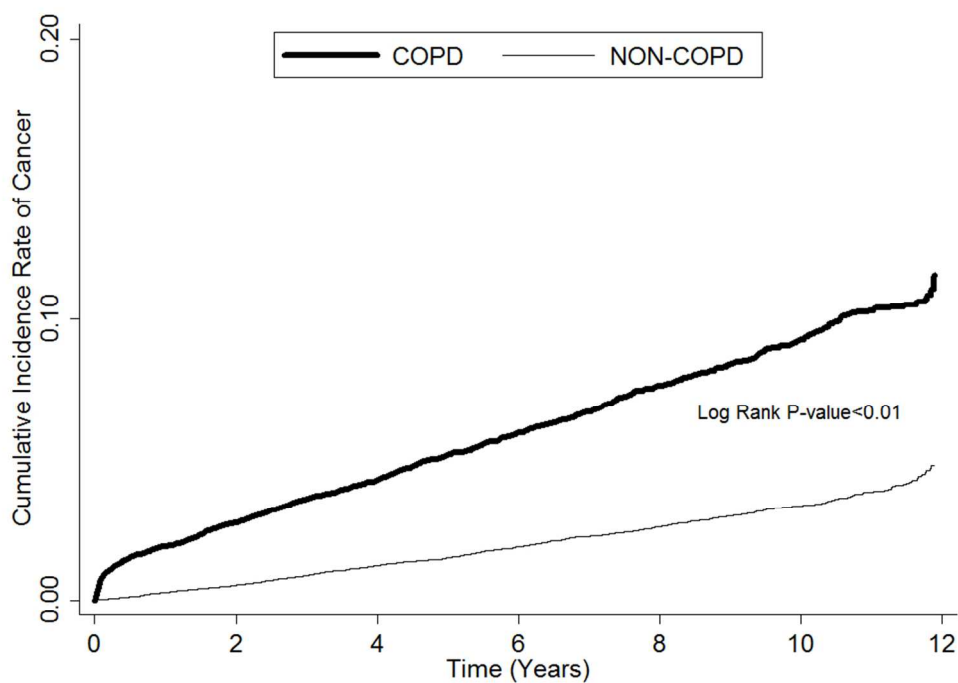


Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

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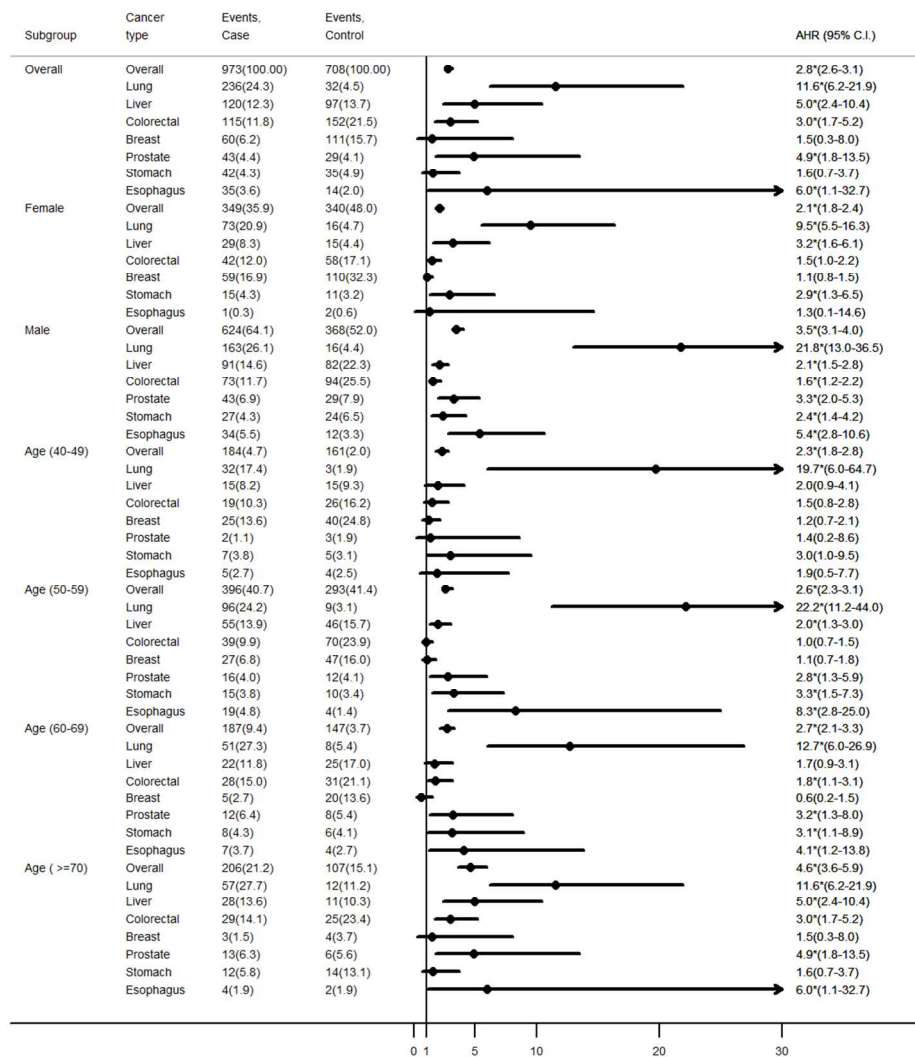


Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

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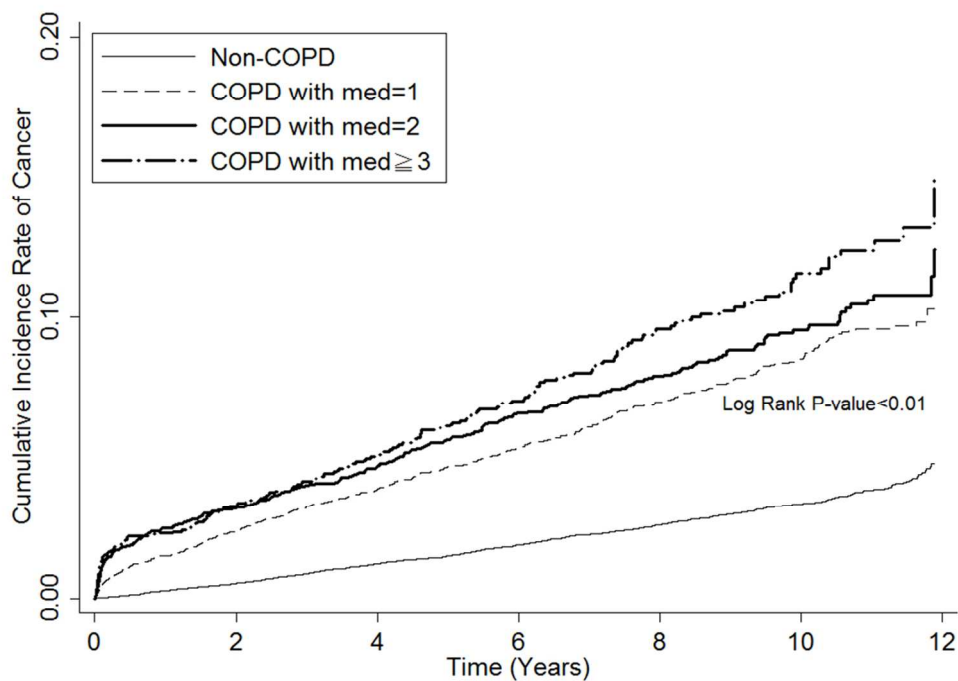


Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

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## STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
		(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
Participants	6	<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	4,5
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	5
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Data sources/measurement	8*	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Bias	9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Study size	10	Describe any efforts to address potential sources of bias	6
Quantitative variables	11	Explain how the study size was arrived at	5,6
		Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	5,6
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7,8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(b) Report category boundaries when continuous variables were categorized	7,8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
<b>Other Information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).