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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 ration; 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 ± standard deviation of patients with COPD was 57.90±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.[1] 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.[2] 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.[3] 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.[4] 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,[4,6-9] 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

type of extra pulmonary cancer. The aim of this study was to exam the incidence of malignant diseases, including specific cancer types, after the diagnosis of COPD compared patients without COPD in Taiwanese patients, using a nationwide cohort database.

Material and Methods:

Ethics Statement

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

Source of data

Taiwan launched a single-payer National Health Insurance (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 in Taiwan was enrolled in the NHI Program. In this study, we analyzed 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 and prescribed COPD medications, including short acting β2 agonists (SABA), long acting β2 agonists (LABA), theophyllines, inhaled corticosteroids (ICS), short-acting muscarinic antagonists (SAMA), Long-acting muscarinic antagonists (LAMA), combination inhaled corticosteroid/long-actingβ2 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC). Patients with COPD was diagnosed between January 1, 2000 and December 31, 2010 and older than 40 years. The index date was the date of the first COPD diagnosis. Patients had a history of malignancy disorders (ICD-9-CM codes 140 to 208) before index date were excluded. During the study period, more than one readmission events may have occurred for the same patient; only the data from the first-time hospitalization record for COPD was analyzed to ensure the independence of observations. In total, 13,470 patients with COPD were retrieved and analyzed.

The control subjects were selected from the remaining patients without COPD and no history of malignancy disease before index date and were matched to the patients with COPD by age and gender. The case: control ratio was 1:2. In total of 26,940 patients without COPD and malignancy

disease were selected as controls. Case and control subject were followed from index date to malignancy diagnosis, death, or the end of study follow up (December 31, 2011), whichever came first.

Definition of Malignancy cases.

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

Comorbidities and medication measures

Baseline comorbidities were assessed before index date for one year. They included chronic kidney disease, liver disease, diabetes, and hyperlipidemia. The ICD-9-CM codes used to define each condition. The Charlson's index[10,11] predicts the mortality for a patient who has a range of comorbid conditions and has been adapted for use with the ICD-9-CM coded administrative database.

COPD medication use on the index date was recorded. We examined use of oral steroid, SABA, LABA, theophyllines, ICS, SAMA, LAMA, ICS/LABA, MTX, and AC.

Statistics

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

Result:

The characteristics and comorbidities of the study subjects are shown in Table 1. There are 13,470 patients with COPD enrolled in the study. The mean age and SD of patients with COPD was 57.9±13.46 years. Ten-year age groups distribution showed that 29.8% were below 49 years of age, 37.53% were 50-59 years, 14.83% were 60-69 years, and 17.77% were 70 years of age or older. The average length of follow-up was 3.87 years from COPD diagnosis to patients with any kind of cancers compared with 5.04 years in control groups. There are 978 patients diagnosed with cancer in patients with COPD. The patients with COPD had a higher prevalence of comorbidities than the control group, including chronic kidney disease, liver disease, diabetes, and dyslipidemia.

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

risk of developing cancer in patients with COPD was associated with the number of COPD medications compared to patients without COPD. The AHR of developing cancer in patients with COPD and used more than 3 kinds of COPD medication was 1.24 (95% CI 1.05-1.47) compared to patients with COPD and only used one kind of COPD medications.

Figure 1 showed the cumulative incidence rate of any types of cancer in patients with or without COPD. Kaplan-Meier analysis was used to compare the patients with or without COPD in the length of time after index date until first occurrence of the cancer. According to the number of medications that are used to treat COPD, we divided patients with COPD into three group and Figure 2 showed their cumulative incidence rate of any types of cancer in patients with or without COPD.

Discussion

Cancer type in patients with COPD

This is the first study to show the common type of cancer among patients with COPD. The most common 5 cancer after COPD diagnosis were: lung cancer, liver cancer, colorectal cancer, prostate cancer and esophagus cancer in male patients and lung cancer, breast cancer, colorectal cancer, liver cancer and stomach cancer in female patients. Patients with COPD had high risk for development of cancer and within a short period of time to get cancer compared to non-COPD population. Patients with COPD had high prevalence of comorbidities compared to the non-COPD population, including chronic kidney disease, liver disease, diabetes, and dyslipidemia. Patients with COPD elevated risk of

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.[12,13] Previous studies[14,15]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.[16] 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.[17]

Liver cancer and COPD

Alpha1-antitrypsin deficiency is one of the common inherited disorders among white persons and predisposed to COPD, cirrhosis and hepatoma.[18,19] Alpha1-antitrypsin deficiency is not an important cause of childhood liver diseases in Southeast Asian population[20]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.[21]

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.[22] 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[23] 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

colorectal cancers can be prevented through regular screening and screening is also crucial in patients with COPD.

Prostate cancer and COPD

It has been noted that dysfunctioning hypothalamic–pituitary–gonadal axis, such as hypogonadotrophic hypogonadism, in patients with COPD.[24,25] The correlation between serum levels of testosterone and risk of prostate cancer is still controversial.[26,27] More recently, a study have implicated patients with COPD have a significant reduction in total and free testosterone compared to the control group.[28] 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.

Aerodigestive cancer and COPD

It is widely accepted that smoking is a risk factor for oropharyngeal cancer, esophagus caner 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

cancer.[29]There is a growing recognition of the importance of systematic examination of the oral cavity, oropharynx and neck which it can detect pre-cancers and cancers at an early and curable stage in patients with COPD and smoking history.

Cancer types in patients with COPD

Our studies show a positive association between COPD and subsequent developing cancer. Compared to those without COPD, patients with COPD had a 55% increased risk for developing cancer (AHR 1.55, 95% CI, 1.48 to 1.62). In previous study of the incidence of cancer, smoking increased the risk of cancer of the oropharynx, upper aerodigestive tract, and lung.[30]From our analysis, in addition to cancer mentioned above, common cancer types includes liver, colon, and breast cancers that are diagnosed with the high frequency in the patients with COPD.

A population-based study[30,31] revealed that 12% of all cancer patients had COPD at the time of cancer diagnosis, being about 15% in age more than 65 years. Besides lung cancer, there is no difference of stage at diagnoses between cancer patients with or without COPD. After using 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.

Limitation

The major limitation was that some of the data, including a history of cigarette smoking, pulmonary function degree of dyspnea, COPD severity and cancer staging were not available from the claims database. We used

the database to demonstrate that COPD was significantly associated with a high risk of cancer, regardless of COPD severity. We also divided COPD population into 3 group according to the number of medications that used to treat COPD to represent the COPD severity. After the stratification, we find that patients used more COPD medications are at higher risk of developing cancer. The study is a nationwide cohort study, and we believe that the large number of participants, the comprehensive enrollment of patients with COPD and longtime followed up ensure that the data are normally distributed and that the results are significant.

Contributorship statement: Chung-Han Ho : acquisition of data, analysis and interpretation of data; Yi-Chen Chen: acquisition of data, analysis of data; Jhi-Joung Wang: contributions to conception and design; Kuang-Ming Liao: drafting the article and final approval of the version to be published.

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Table 1 Demographic Characteristics and Comorbidities in Patients with/without COPD

	COPD N(%)	Non-COPD N(%)	P-value
	N=13470	N=26940	
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)
Number of COPD								

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)

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

	Crude HR [a] (95% CI [a])	P-value	†AHR [b] (95% CI [a])	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

[a] HR=hazard ratio; CI= confidence interval

[b] AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustment for age, sex, and comorbidities.

Table4. Hazard ratio of developing cancer in relation to baseline characteristics and COPD medications of the study subjects

	AHR [b] with COPD medications (95% CI [a])	P-value	†AHR [b] for COPD only (95% CI [a])	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

[a] CI= confidence interval

[b] 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

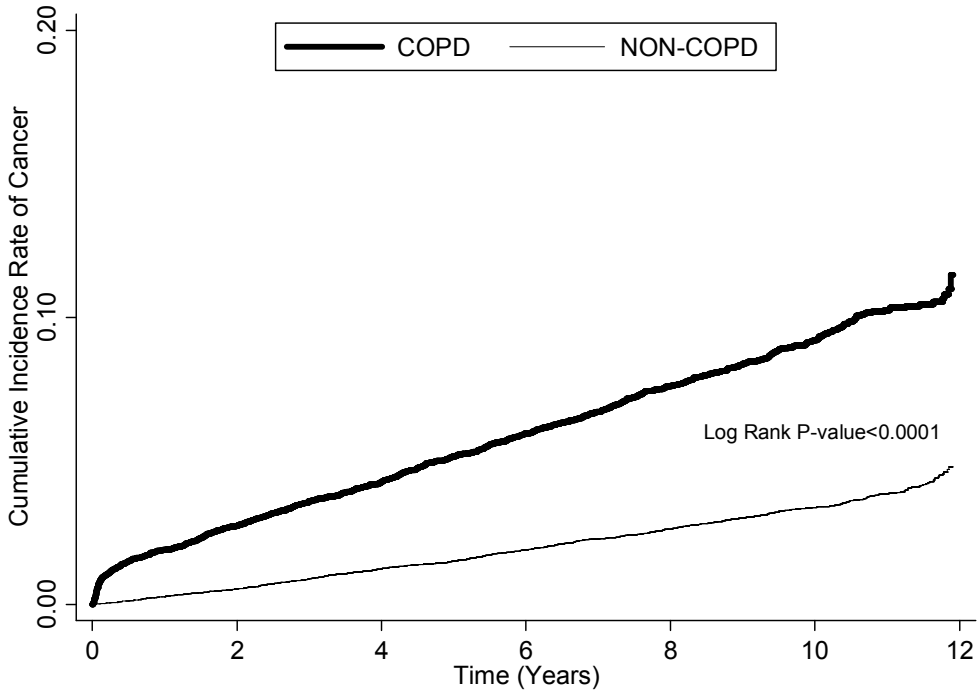
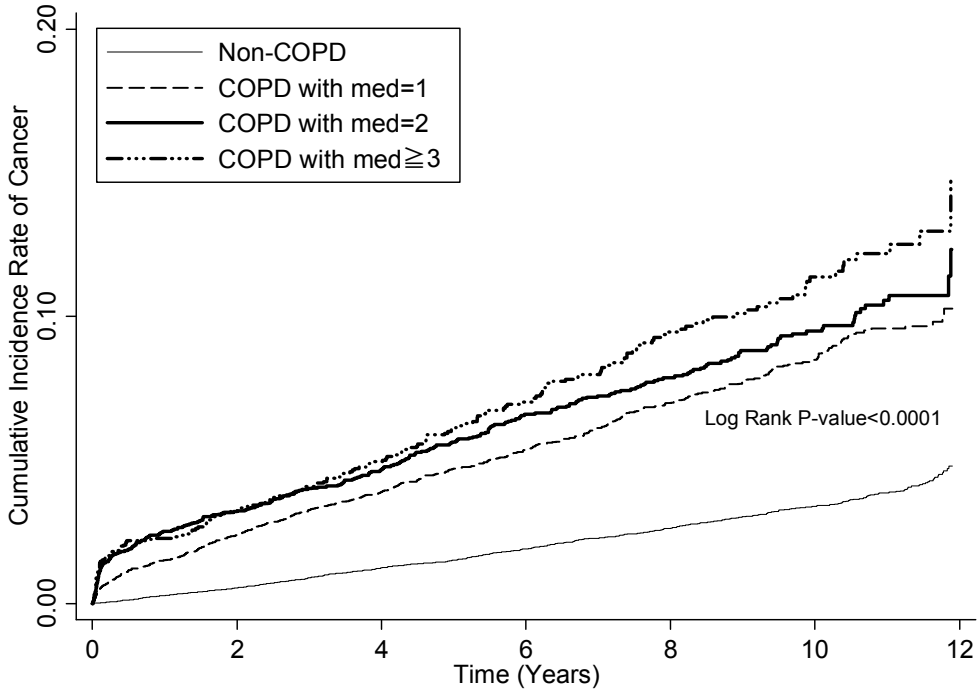


Figure2. Cumulative incidence rate in COPD patients with different medications.



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
Introduction			
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
Methods			
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
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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	
Discussion			
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
Other Information			
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.

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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.

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,

496) or at least three ambulatory visits for COPD who was also prescribed COPD medications, including short acting β2 agonists (SABA), long-acting β2 agonists (LABA), theophylline, inhaled short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists (LAMA), combination inhaled corticosteroid/long-acting β2 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC). Included patients were those over 40 years of age who received a diagnosis of COPD between January 1, 2000 and December 31, 2010. The index date was the date of the first COPD diagnosis. Patients with a history of malignancy disorders (ICD-9-CM codes 140 to 208) before the index date were excluded. During the study period, more than one readmission event may have occurred for the same patient; only the data from the first-time hospitalization record for COPD were analysed to ensure the independence of observations. In total, 13,289 patients with COPD were retrieved and analysed.

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

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

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

Result:

The characteristics and comorbidities of the study subjects are shown in Table 1. Overall, 13,470 patients with COPD enrolled in the study. The mean age±SD of the COPD patients was 57.9±13.5 years. A ten-year age group distribution showed that 29.7% were 49 years of age or younger, 37.6% were 50-59 years, 14.9% were 60-69 years, and 17.8% were 70 years of age or older. The average length of follow-up was 3.9 years from COPD diagnosis to patients being diagnosed with any type of cancers compared with 5.0 years in the control groups ($p<0.01$). Patients with

COPD were diagnosed with cancer (n=973, 73%) at significantly higher rates than patients without COPD (n=708, 2.7%) (p<0.01). The patients with COPD had a higher prevalence of comorbidities than the control group (p<0.01), including cardiovascular disease, chronic kidney disease, liver disease, diabetes, and dyslipidaemia.

Figure 1 shows the cumulative incidence rate of any type of cancer in patients with or without COPD from the index date until the first occurrence of the cancer using Kaplan-Meier methods. The patients with COPD had higher cancer incidence rates compared with patients without COPD (log-rank test: p<0.01). Table 2 shows that the adjusted HR of developing cancer among patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients without COPD after adjusting for age, sex, and comorbidities. For comparing the risk of cancer among each of the seven cancer types between COPD and non-COPD patients, the adjusted hazard ratios for each cancer type are reported in Figure 2. Patients with COPD had significantly higher risks of lung (AHR: 11.6; 95% C.I.: 6.2-21.9), liver (AHR: 5.0; 95% C.I.: 2.4-10.4), colorectal (AHR: 3.0; 95% C.I.: 1.7-5.2), prostate (AHR: 4.9; 95% C.I.: 1.8-13.5), and oesophageal (AHR: 6.0; 95% C.I.: 1.1-32.7) cancer. Moreover, the stratified analysis of the cancer risk between COPD and non-COPD patients by age group and sex for any type of cancer and each of the seven cancer types is also presented (Figure 2).

Patients with COPD were divided into three groups according to the number of medications used to treat COPD, and Figure 3 shows the cumulative incidence rates of any type of cancer in patients with or

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

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

Lung cancer and COPD

Both COPD and lung cancer have high morbidity and mortality rates worldwide.[9, 10] Previous studies[11, 12] have shown that patients with COPD are at increased risk for the development of lung cancer, and lung cancer is an important cause of death in patients with COPD.[13] Patients with COPD are at increased risk for lung cancer because most of them have a history of smoking. Additionally, patients with COPD are of lower socioeconomic status compared to the general population, and socioeconomic status may affect quality of life, including environmental

exposure to indoor and outdoor air pollution; these factors may influence the development of lung cancer.

Chronic inflammation after extracellular stimulation, such as tobacco smoking and 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.[14]

Liver cancer and COPD

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

Colorectal cancer and COPD

Colorectal cancer is one of the most common cancers in patients with COPD.[19] Patients with COPD experienced sensations of dyspnoea in their daily activities, and consequently tended to lead more sedentary lifestyles; sedentary behavior may also increase the risk of colorectal cancer. A nationwide population-based observational study investigated

the influence of COPD on intensive care unit admissions, medication treatments, and mortality following colorectal cancer surgery.[20] The authors identified 7.9% of colorectal cancer surgery patients as having a COPD diagnosis, and in this population, more complications were noted after surgery, including higher ICU admission rates, more frequent need for mechanical ventilation, higher rates of requiring reoperation, and more frequent inotropes/vasopressors. The 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[21] 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 benefits after receipt of adjuvant therapy. Although COPD appeared to be a barrier to chemotherapy, chemotherapy can provide a survival benefit to patients who have colon cancer with COPD. Many colorectal cancers can be prevented through regular screening, and screening is also crucial in patients with COPD.

Prostate cancer and COPD

Dysfunction in the hypothalamic–pituitary–gonadal axis, such as hypogonadotropic hypogonadism, has been noted in patients with COPD.[22, 23] The correlation between serum levels of testosterone and risk of prostate cancer is still controversial.[24, 25] One recent study

found that patients with COPD had a significant reduction in total and free testosterone levels compared to controls.[26] The relationship between testosterone level and prostate cancer in patients with COPD needs further investigation. In our study, more than 80% of prostate cancers were diagnosed in men who were 60 years of age or older. A prostate-specific antigen-based screening test for prostate cancer may be warranted in the elderly male population with COPD.

Aerodigestive cancer and COPD

It is widely accepted that smoking is a risk factor for oropharyngeal cancer, oesophageal cancer, and COPD. In our study, development of cancers of the upper aerodigestive tract, including oropharyngeal and oesophageal cancers, were 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 the risk of COPD and aerodigestive tract and lung cancers.[27] In addition to the same risk factor of smoking, the higher risk of aerodigestive cancers in COPD patients can be partially explained by socioeconomic status. A previous study showed that the risk of aerodigestive cancers cannot be entirely explained by smoking, alcohol consumption, and diet. Socioeconomic status was also a risk factor for upper aerodigestive tract cancers.[28] There is growing recognition of the importance of systematic examination of the oral cavity, oropharynx, and neck, which can detect pre-cancers and cancers at an early and curable

stage in patients with COPD with a history of smoking.

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 analysed prescription patterns, including prescriptions of bronchodilators

and steroids, in all patients with COPD from January 1, 2000 to December 31, 2011, utilizing stricter inclusion criteria of patients over 40 years old who had attended at least three ambulatory medical visits for COPD. In our study, we analysed the comorbidities of patients with and without COPD and the hazard ratio of developing cancer in relation to the baseline characteristics, which were not performed in the Chiang et al. study. We also found that the risk of developing cancer was higher when more bronchodilators were used. If patients with COPD use more than two bronchodilators, representing COPD severity, the disease severity of COPD may be associated with increased cancer risk. In summary, in Chiang's study, the researchers included patient over 20 years of age, while we enrolled patients aged over 40 years. The COPD patients in our study were treated with COPD medications, and the non-COPD groups were not treated with any COPD medications. In Chiang's study, they did not survey COPD medications. Our study participants were exactly matched by age and gender, and their comorbidities were analysed using the Cox model. In Chiang's study, they used SIR to analyse the risk of cancer. SIR cannot adjust for comorbidities or medications.

Kornum et al.[30] used the Danish National Registry of Patients and their nationwide cancer registry databases to show the incidence of various cancers in 236,494 patients with COPD from 1980 to 2008. They included patients aged 40 years or older with COPD. Patients were enrolled after a first-time hospitalization, outpatient clinic visit or a visit to an emergency department with a diagnosis of COPD from ICD-8 or IC-10 codes. The researchers focused on tobacco-related and

alcohol-related cancers, but they did not evaluate comorbidities and medications in patients with COPD. They found that lung, aerodigestive and liver cancers were increased in patients with COPD.

Limitations

One major limitation was that some of the data, including histories of cigarette smoking, pulmonary function, degree of dyspnoea, COPD severity, and cancer staging, were not available from the claims database. We used the database to demonstrate that COPD was significantly associated with a high risk of cancer, regardless of COPD severity. As a representation of COPD severity, we also divided the COPD population into 3 groups according to the number of medications they used to treat COPD. After the stratification, we found that patients who used more COPD medications were at a higher risk of developing cancer. Other limitations should be acknowledged, including that the data were based on insurance records that lacked consideration of other factors associated with COPD and cancer, such as lifestyle choices, physical activity, and socioeconomic status, which may have led to possible errors. The limitations of the analysis based on the database include an inability to truly characterize the patients and controls.

The study was a nationwide cohort study; we believe that the large number of participants, the comprehensive enrolment of patients with COPD, and the long-term follow-up ensured that the data are normally distributed and that the results are significant.

Conclusion

In addition to lung cancer, patients with COPD have a higher risk of developing other types of cancer, and physicians should closely monitor and follow up with these patients.

Contribution statement: Chung-Han Ho: acquisition of data, analysis and interpretation of data; Yi-Chen Chen: acquisition and analysis of data; Jhi-Joung Wang: contributions to conception and design; Kuang-Ming Liao: drafting the article and final approval of the version to be published.

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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 [a] (95% CI [a])	P-value	†AHR [b] (95% CI [a])	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

[a] HR=hazard ratio; CI= confidence interval

[b] 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 [b] of cancer among all study subjects (95% CI [a])	P-value	†AHR [b] of cancer for patients with COPD only (95% CI [a])	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

[a] CI=confidence interval

[b] AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustments for age, sex, and comorbidities.

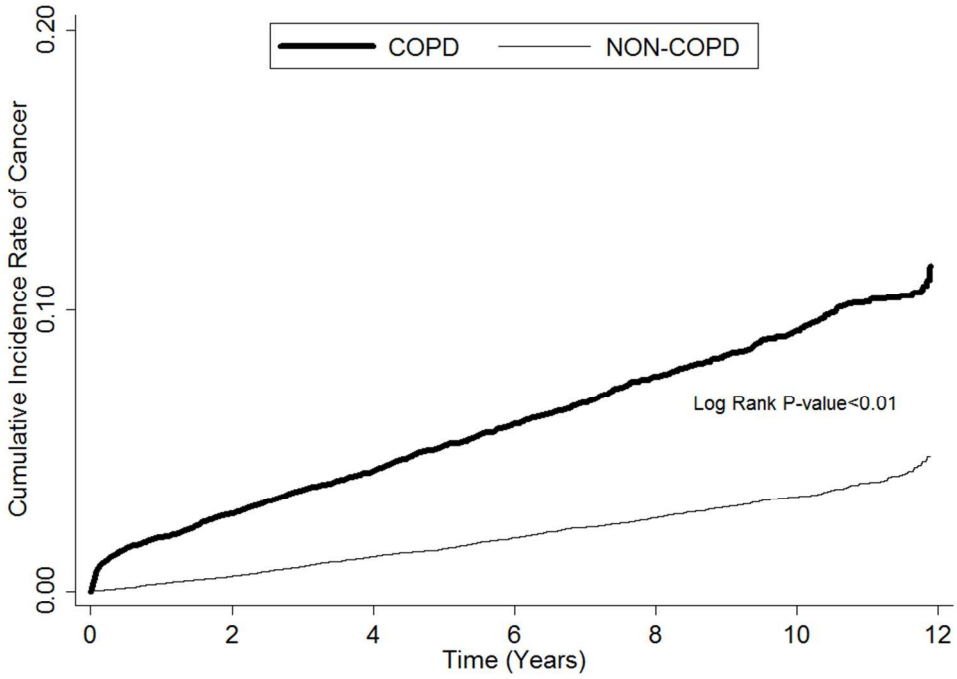

Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

85x60mm (300 x 300 DPI)

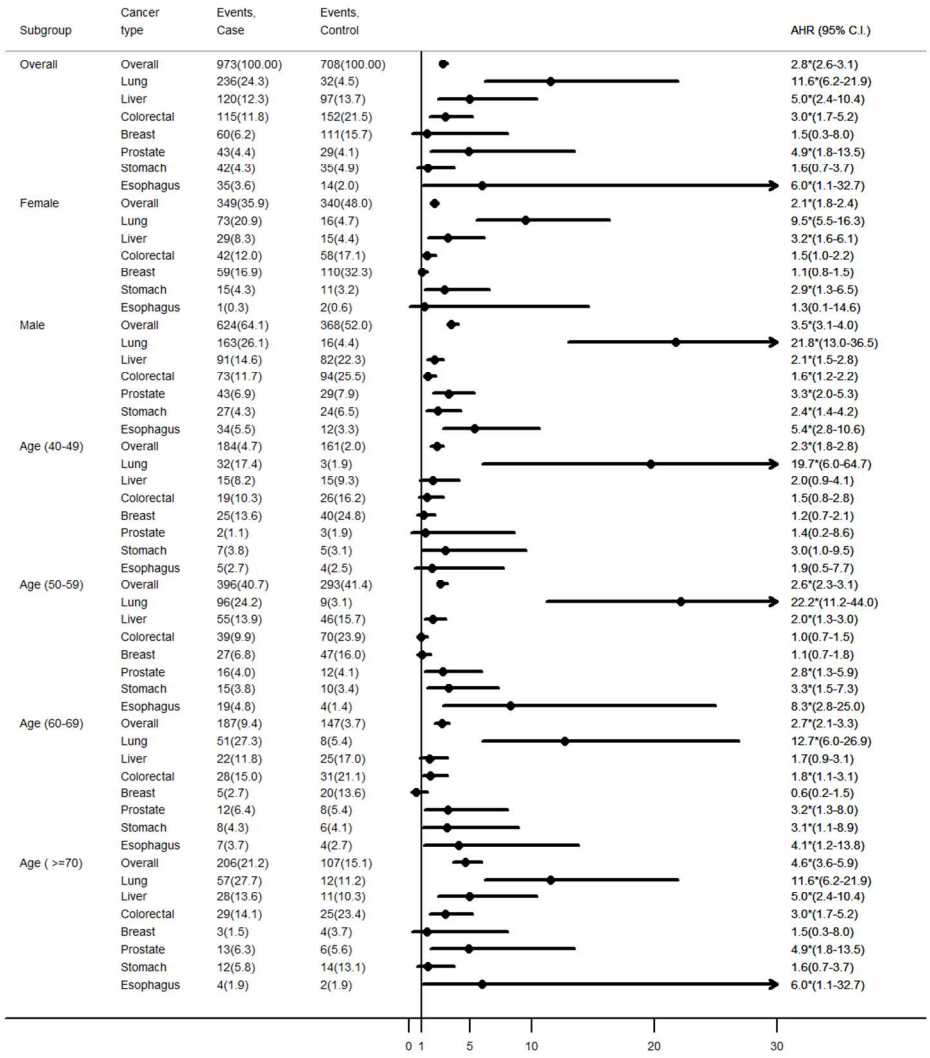

Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

101x115mm (300 x 300 DPI)

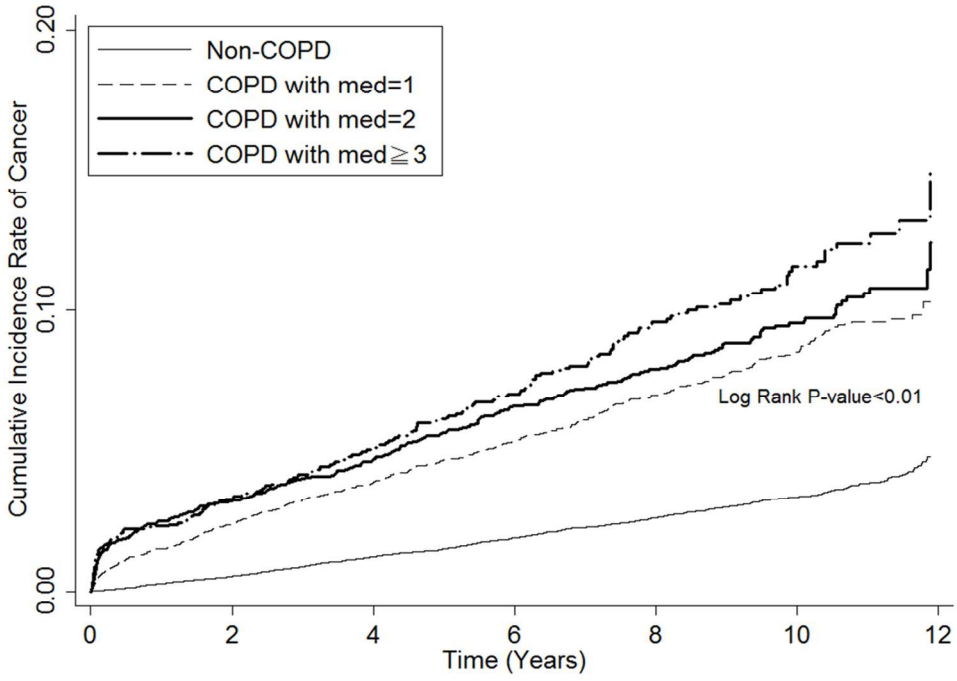

Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

101x72mm (300 x 300 DPI)

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
Introduction			
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
Methods			
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
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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	
Discussion			
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
Other Information			
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.

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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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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 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

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, 496) or at least three ambulatory visits for COPD who was also

prescribed COPD medications, including short acting β2 agonists (SABA), long-acting β2 agonists (LABA), theophylline, inhaled short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists (LAMA), combination inhaled corticosteroid/long-acting β2 agonist (ICS/LABA), methylxanthines (MTX), and anticholinergics (AC). Included patients were those over 40 years of age who received a diagnosis of COPD between January 1, 2000 and December 31, 2010. The index date was the date of the first COPD diagnosis. Patients with a history of malignancy disorders (ICD-9-CM codes 140 to 208) before the index date were excluded. During the study period, more than one readmission event may have occurred for the same patient; only the data from the first-time hospitalization record for COPD were analysed to ensure the independence of observations. In total, 13,289 patients with COPD were retrieved and analysed.

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

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

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

Result:

The characteristics and comorbidities of the study subjects are shown in Table 1. Overall, 13,289 patients with COPD enrolled in the study. The mean age±SD of the COPD patients was 57.9±13.5 years. A ten-year age group distribution showed that 29.7% were 49 years of age or younger, 37.6% were 50-59 years, 14.9% were 60-69 years, and 17.8% were 70 years of age or older. The average length of follow-up was 3.9 years from COPD diagnosis to patients being diagnosed with any type of cancers compared with 5.0 years in the control groups (p<0.01). Patients with COPD were diagnosed with cancer (n=973, 73%) at significantly higher

rates than patients without COPD (n=708, 2.7%) (p<0.01). The patients with COPD had a higher prevalence of comorbidities than the control group (p<0.01), including cardiovascular disease, chronic kidney disease, liver disease, diabetes, and dyslipidaemia.

Figure 1 shows the cumulative incidence rate of any type of cancer in patients with or without COPD from the index date until the first occurrence of the cancer using Kaplan-Meier methods. The patients with COPD had higher cancer incidence rates compared with patients without COPD (log-rank test: p<0.01). Table 2 shows that the adjusted HR of developing cancer among patients with COPD was 2.8 (95% CI: 2.6-3.1) compared to patients without COPD after adjusting for age, sex, and comorbidities. For comparing the risk of cancer among each of the seven cancer types between COPD and non-COPD patients, the adjusted hazard ratios for each cancer type are reported in Figure 2. Patients with COPD had significantly higher risks of lung (AHR: 11.6; 95% C.I.: 6.2-21.9), liver (AHR: 5.0; 95% C.I.: 2.4-10.4), colorectal (AHR: 3.0; 95% C.I.: 1.7-5.2), prostate (AHR: 4.9; 95% C.I.: 1.8-13.5), and oesophageal (AHR: 6.0; 95% C.I.: 1.1-32.7) cancer. Moreover, the stratified analysis of the cancer risk between COPD and non-COPD patients by age group and sex for any type of cancer and each of the seven cancer types is also presented (Figure 2).

Patients with COPD were divided into three groups according to the number of medications used to treat COPD, and Figure 3 shows the cumulative incidence rates of any type of cancer in patients with or 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 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

patients with COPD. The five most common cancers after COPD diagnosis included: lung cancer, liver cancer, colorectal cancer, prostate cancer, and oesophageal cancer in male patients and lung cancer, breast cancer, colorectal cancer, liver cancer, and stomach cancer in female patients. Patients with COPD had a higher risk of developing cancer and developed cancer within a shorter period of time compared with the non-COPD population. Patients with COPD had a high prevalence of comorbidities compared to the non-COPD population, including chronic kidney disease, liver disease, diabetes, and dyslipidaemia. Patients with COPD had an elevated risk of developing cancer when they used more types of COPD medications compared with the non-COPD population. In patients with COPD, the risk of developing cancer was significant when they used more than two types of COPD medications compared to the COPD patients who only used one type of COPD medication.

Lung cancer and COPD

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

the development of lung cancer.

Chronic inflammation after extracellular stimulation, such as tobacco smoking and 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.[14]

Liver cancer and COPD

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

Colorectal cancer and COPD

Colorectal cancer is one of the most common cancers in patients with COPD.[19] Patients with COPD experienced sensations of dyspnoea in their daily activities, and consequently tended to lead more sedentary lifestyles; sedentary behavior may also increase the risk of colorectal cancer. A nationwide population-based observational study investigated the influence of COPD on intensive care unit admissions, medication

treatments, and mortality following colorectal cancer surgery.[20] The authors identified 7.9% of colorectal cancer surgery patients as having a COPD diagnosis, and in this population, more complications were noted after surgery, including higher ICU admission rates, more frequent need for mechanical ventilation, higher rates of requiring reoperation, and more frequent inotropes/vasopressors. The 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[21] 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 benefits after receipt of adjuvant therapy. Although COPD appeared to be a barrier to chemotherapy, chemotherapy can provide a survival benefit to patients who have colon cancer with COPD. Many colorectal cancers can be prevented through regular screening, and screening is also crucial in patients with COPD.

Prostate cancer and COPD

Dysfunction in the hypothalamic–pituitary–gonadal axis, such as hypogonadotropic hypogonadism, has been noted in patients with COPD.[22, 23] The correlation between serum levels of testosterone and risk of prostate cancer is still controversial.[24, 25] One recent study found that patients with COPD had a significant reduction in total and

free testosterone levels compared to controls.[26] The relationship between testosterone level and prostate cancer in patients with COPD needs further investigation. In our study, more than 80% of prostate cancers were diagnosed in men who were 60 years of age or older. A prostate-specific antigen-based screening test for prostate cancer may be warranted in the elderly male population with COPD.

Aerodigestive cancer and COPD

It is widely accepted that smoking is a risk factor for oropharyngeal cancer, oesophageal cancer, and COPD. In our study, development of cancers of the upper aerodigestive tract, including oropharyngeal and oesophageal cancers, were 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 the risk of COPD and aerodigestive tract and lung cancers.[27] In addition to the same risk factor of smoking, the higher risk of aerodigestive cancers in COPD patients can be partially explained by socioeconomic status. A previous study showed that the risk of aerodigestive cancers cannot be entirely explained by smoking, alcohol consumption, and diet. Socioeconomic status was also a risk factor for upper aerodigestive tract cancers.[28] There is growing recognition of the importance of systematic examination of the oral cavity, oropharynx, and neck, which can detect pre-cancers and cancers at an early and curable stage in patients with COPD with a history of smoking.

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

with stricter inclusion criteria which aged more than 40 years and visit at least three ambulatory visits for COPD. In our study, we analyzed the comorbidities in patients with and without COPD and hazard ratio of developing cancer in relation to baseline characteristics which did not performed in Chiang et al. study. We also found that the more bronchodilators patients with COPD used, the more risk of developing cancer. If patients with COPD used more than 2 bronchodilators representing COPD severity, the disease severity of COPD may be associated with increasing cancer risk.

In summary, in Chiang's study, they included patient aged more than 20 years. We enrolled patient aged more than 40 years. The COPD patients in our study were treated with COPD medications and non-COPD groups did not treated with any COPD medications. In Chiang's study, they did not survey the COPD medications. Our study exactly match by age and gender with Cox model and analyzed the comorbidities. In Chiang's study, they used SIR to analyze the risk of cancer. SIR cannot adjust comorbidity and medications.

In figure 2, consistent with the results of Chiang's studies, patients with COPD had a higher risk of lung, aerodigestive and prostate cancer. There was difference in association between COPD and cancers in our study compared to Chiang's study after adjusting for age and gender. In our study, patients with COPD had a higher risk of liver and colorectal cancer compared to patients without COPD. Although the risk of head and neck cancer was higher in patients with COPD compared to general population in Chiang's study, there was no significant difference risk in our study

after adjusting for age and gender. In addition to lung and aerodigestive cancer, we suggest that patients with COPD follow-up cancer screening may include liver and colorectal cancer.

Kornum et al.[30] used the Danish National Registry of Patients and their nationwide cancer registry databases to show the incidence of various cancers in 236,494 patients with COPD from 1980 to 2008. They included patients aged 40 years or older with COPD. Patients were enrolled after a first-time hospitalization, outpatient clinic visit or a visit to an emergency department with a diagnosis of COPD from ICD-8 or IC-10 codes. The researchers focused on tobacco-related and alcohol-related cancers, but they did not evaluate comorbidities and medications in patients with COPD. They found that lung, aerodigestive and liver cancers were increased in patients with COPD.

Limitations

One major limitation was that some of the data, including histories of cigarette smoking, pulmonary function, degree of dyspnoea, COPD severity, and cancer staging, were not available from the claims database. We used the database to demonstrate that COPD was significantly associated with a high risk of cancer, regardless of COPD severity. As a representation of COPD severity, we also divided the COPD population into 3 groups according to the number of medications they used to treat COPD. After the stratification, we found that patients who used more COPD medications were at a higher risk of developing cancer. Other limitations should be acknowledged, including that the data were based

on insurance records that lacked consideration of other factors associated with COPD and cancer, such as lifestyle choices, physical activity, and socioeconomic status, which may have led to possible errors. The limitations of the analysis based on the database include an inability to truly characterize the patients and controls.

The study was a nationwide cohort study; we believe that the large number of participants, the comprehensive enrolment of patients with COPD, and the long-term follow-up ensured that the data are normally distributed and that the results are significant.

Conclusion

In addition to lung cancer, patients with COPD have a higher risk of developing other types of cancer, and physicians should closely monitor and follow up with these patients.

Contribution statement: Chung-Han Ho: acquisition of data, analysis and interpretation of data; Yi-Chen Chen: acquisition and analysis of data; Jhi-Joung Wang: contributions to conception and design; Kuang-Ming Liao: drafting the article and final approval of the version to be published.

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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 [a] (95% CI [a])	P-value	†AHR [b] (95% CI [a])	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

[a] HR=hazard ratio; CI= confidence interval

[b] 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 [b] of cancer among all study subjects (95% CI [a])	P-value	†AHR [b] of cancer for COPD patients alone (95% CI [a])	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

[a] CI=confidence interval

[b] AHR=adjusted hazard ratio; based on Cox proportional hazard regression model with adjustments for age, sex, and comorbidities.

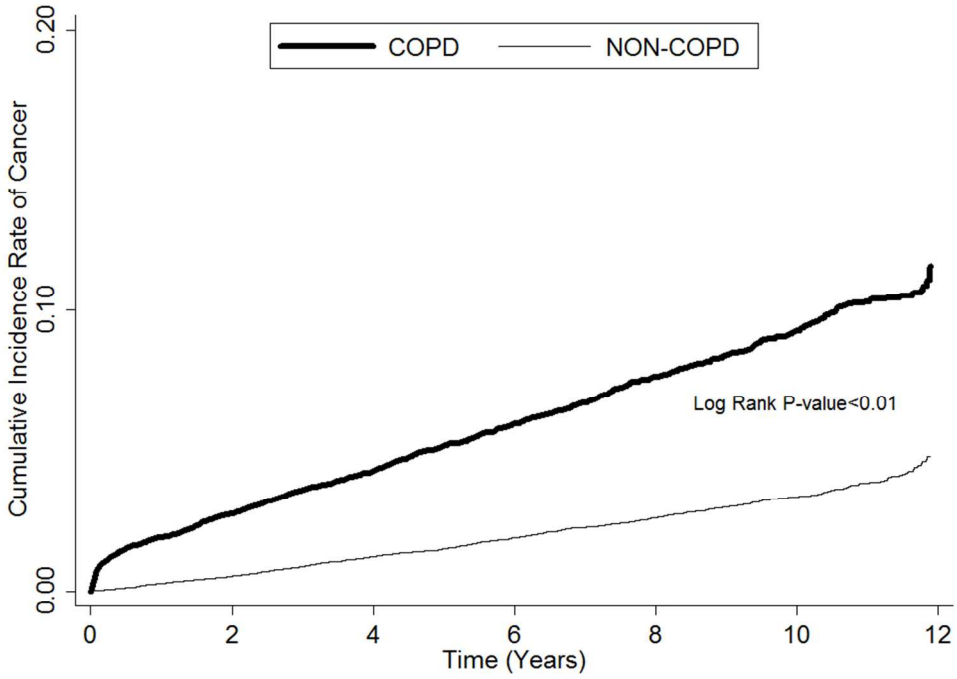

Figure 1. Kaplan-Meier plot for cancer incidence between COPD patients and non-COPD patients.

85x60mm (300 x 300 DPI)

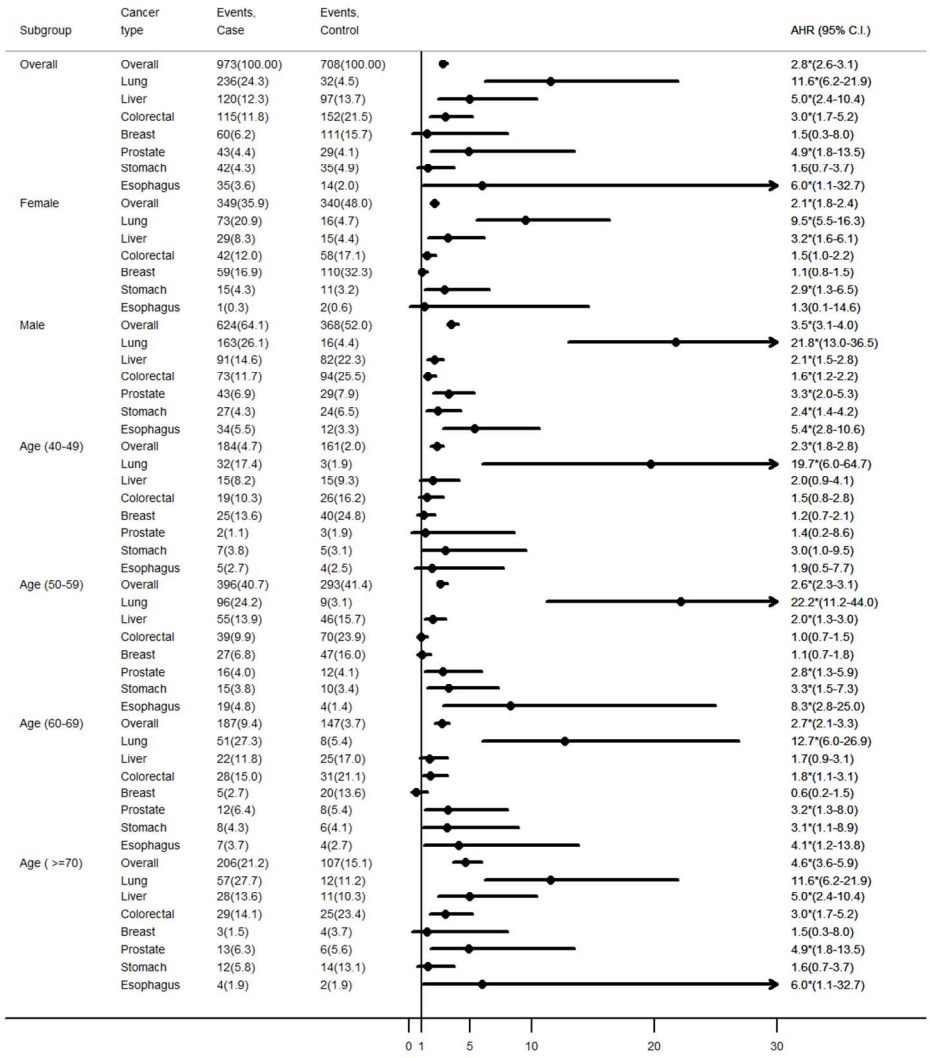

Figure 2. The overall and stratified analyses for the incidence and hazard ratio of developing cancer between patients with COPD and patients without COPD among any type of cancer and the seven major cancer types.

101x115mm (300 x 300 DPI)

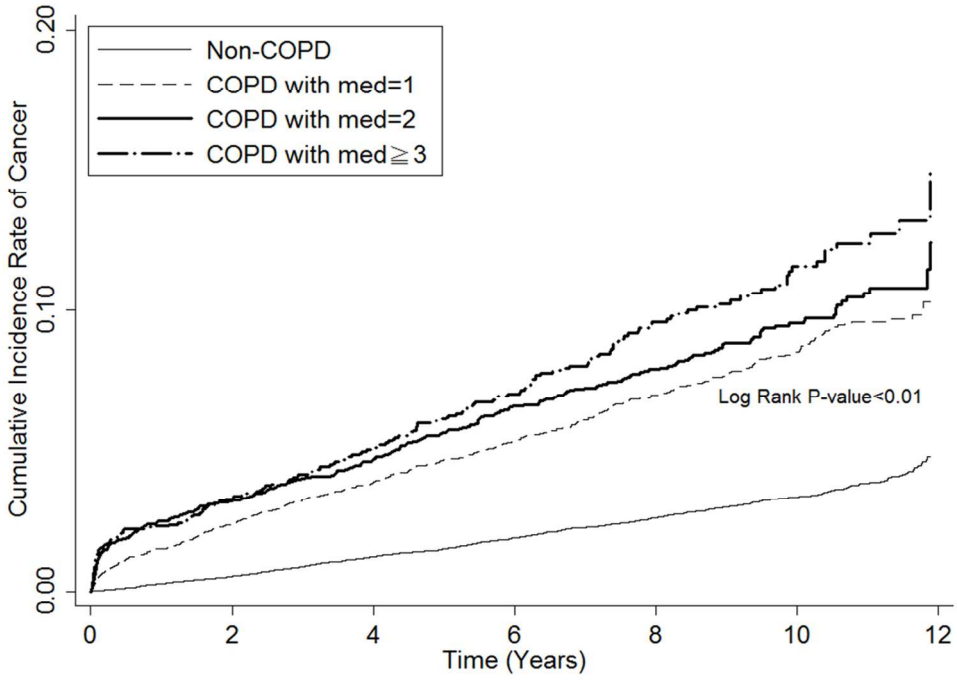

Figure 3. Kaplan-Meier plot of cumulative incidence rates of cancer among COPD patients with different medications and patients without COPD.

101x72mm (300 x 300 DPI)

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
Introduction			
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
Methods			
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
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/measurement	8*	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
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7,8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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	
Discussion			
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
Other Information			
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.