

# Effect of annual influenza vaccination on reducing lung cancer in patients with chronic obstructive pulmonary disease from a population-based cohort study

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## Abstract

Chronic obstructive pulmonary disease (COPD) patients are at a higher risk of development of lung cancer. Frequent exacerbations of COPD trigger the disease course to chronic inflammation which likely plays a role in the pathogenesis of lung cancer. Previous studies showed influenza virus infection is one of important causes for exacerbations of COPD. Therefore, the aim of this study was to know whether influenza vaccination could reduce the incidence of lung cancer in patients with COPD.

This cohort study enrolled patients ( $\geq 55$  years old) with a recorded diagnosis of COPD between January 1, 2000 and December 31, 2012 by using the Taiwan Health Insurance Database. A propensity score was calculated to reduce vaccine therapy selection bias. Cox proportional hazard regressions were used to investigate the association between the influenza vaccination and lung cancer incidence after adjusting for known confounding factors. Besides, we categorized the patients into 4 groups according to vaccination status (unvaccinated, total number of vaccinations: 1, 2–3,  $\geq 4$ ) to evaluate the dose-dependent effect on reducing lung cancer occurrence of lung cancer in COPD patients.

Our study comprised of 28,752 eligible individuals from the COPD cohort database. Among them, 51% (14,630) received influenza vaccination; the rest (49%) of the COPD patients did not receive influenza vaccination. We observed that COPD patients receiving influenza vaccination had a lower risk of lung cancer (adjusted HR=0.40, 95% CI (0.35–0.45),  $P < .001$ ). We also founded comparable protective effect in both sexes and all age groups (55–64, 65–74,  $\geq 75$ ) regardless of influenza seasonality. Furthermore, dose-dependent protective effect could be seen after stratifying patients according to the total number vaccinations, the adjusted HRs for lung cancer risk were 0.48 (0.40–0.54) and 0.24 (0.20–0.29) for patients who received 2 to 3 and  $\geq 4$  vaccinations during the follow-up period.

This population-based cohort study demonstrated that annual influenza vaccination administration could reduce incidence of lung cancer in COPD patients.

**Abbreviations:** CCI = Charlson Comorbidity Index, CI = confidence interval, COPD = Chronic obstructive pulmonary disease, DNA = deoxyribonucleic acid, HBV = hepatitis B, HPV = human papillomavirus, HR = hazard ratio, ICD-9-CM = The International Statistical Classification of Diseases and Related Health Problems 9th, clinical modification, ICS = inhaled corticosteroid, NAC = N-acetyl cysteine, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PS = propensity scores, RNOS = reactive nitrogen and oxygen species, T<sub>H</sub>1 = T helper 1, T<sub>H</sub>2 = T helper 2.

**Keywords:** chronic obstructive pulmonary disease, frequent exacerbations, influenza vaccination, lung cancer

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KYC and SMW contributed equally to this study.

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## 1. Introduction

Both chronic obstructive pulmonary disease (COPD) and lung cancer are major smoking-related diseases leading to morbidity and mortality worldwide.<sup>[1]</sup> Epidemiological studies showed COPD was associated with an increase in risk of lung cancer,<sup>[2,3]</sup> on the other hand, 50% to 70% lung cancer patients diagnosed with airflow obstruction evidence of COPD.<sup>[4]</sup> Furthermore, a significant proportion of 33% patients with COPD died of lung cancer over a 14.5-year follow up.<sup>[5]</sup> Currently, it remains unclear the exact mechanisms underlying the higher incidence of lung cancer in patients with COPD. However, progress of research findings on pathogenesis of linking these 2 diseases help to discover chemo-preventive or chemotherapeutic targets in recent years.

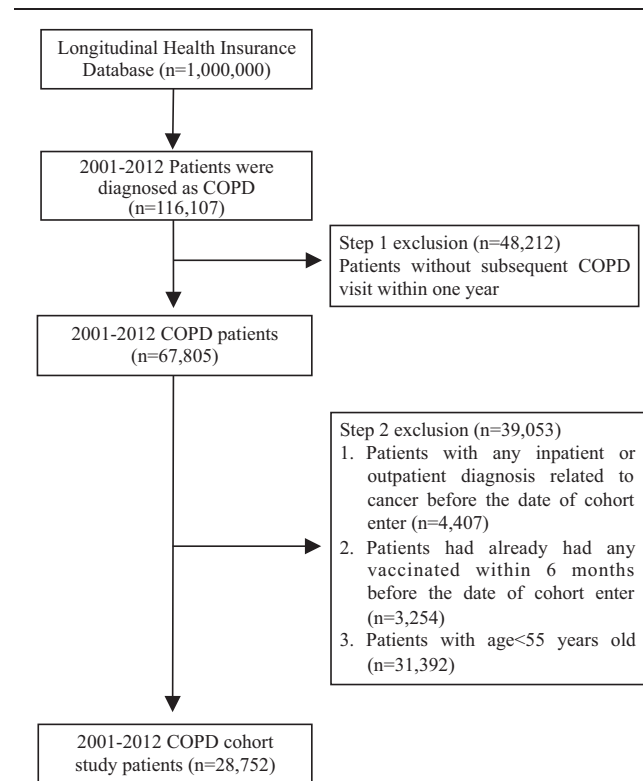
Un-resolving inflammation was a key shared pathogenesis of both COPD and lung cancer, and repeated or chronic airway infections was thought to be one important underlying mechanism. Exacerbations are characteristic of the clinical course of COPD with closely link to persistent amplifying inflammation. Virus infection is one of predominant causes for frequent exacerbations. Rhinoviruses are most common viruses related to exacerbations of COPD but influenza is more common in severe exacerbations necessary for admission.<sup>[6]</sup> In view of lung cancer, main risk factors such as cigarette smoking, environmental pollution, radiation, and exposure to asbestos have been implicated and virus like human papillomavirus (HPV) represents an additional one.<sup>[7]</sup> HPV vaccine is reasonable to be introduced to reduce incidence of HPV cervical and other HPV-related cancers including lung cancer but only effective in cervical cancer prevention reported currently.<sup>[8]</sup>

Considering lung cancer occurred in COPD patients, possibly frequent exacerbations resulted from repeated or chronic viruses infections drove carcinogenesis of lung, we addressed the question whether available influenza vaccination could reduce lung cancer incidence in COPD patients. To clarify the potential protective benefit of influenza vaccination on occurrence of lung cancer in Taiwanese patients with COPD, we performed a population-based cohort study using reimbursement claims from Taiwan's National Health Insurance Research Database (NHIRD).

## 2. Materials and methods

The National Health Insurance (NHI) program has been established since 1995 to provide comprehensive health insurance consist of all of Taiwan residents. Nowadays, 98% of the more than 23 million people are covered under the NHI. We analyzed information obtained from the Taiwan NHIRD 2001 to 2012. There were no statistically significant differences in age, sex, or healthcare costs between the sample group and all enrollees. Influenza season was defined as the interval during October to March according to Taiwan Center of Disease Control. The study was approved by the Joint Institutional Review Board of Taipei Medical University (approval no. N201708051).

This study screens all patients who visited healthcare facilities in Taiwan with diagnosis of COPD (International Classification of Disease, the 9th Revision, Clinical Modification Code) over a 12-year period ( $n = 116,107$ ) from January 1, 2000 to December 31, 2012. Patients without subsequent COPD visit within one year were excluded ( $n = 45,009$ ) due to be considered no chronic pulmonary disease (Fig. 1). We also excluded 39,053 patients as following criteria:



**Figure 1.** The process of patient selection from a representative database from National Health Research Institute of Taiwan 1,000,000 subjects from year 2001 to 2012 registry of all NHI database for inclusion. COPD=chronic obstructive pulmonary disease.

Patients with any inpatient or outpatient diagnosis related to cancer before the date of cohort enter ( $n = 4,407$ ),

Individuals had already any vaccinated within 6 months before the date of cohort enter ( $n = 3,254$ ) and

Patients with age <55 years old ( $n = 31,392$ ).

The indication of receiving administration of influenza vaccination in Taiwan are those high-risk elderly population (people aged  $\geq 50$  with type 2 diabetes, chronic liver infection of liver cirrhosis, cardiovascular diseases, or chronic pulmonary disease) since 1998, and for all adults older than 65 years since 2001.<sup>[9]</sup> The vaccination status was recognized by code V048 and/or the use of vaccine (confirmed by drug codes). Each patient was reviewed for the Charlson Comorbidity Index (CCI) and risk factors for CAD (the main co-morbidity of COPD): hypertension, diabetes mellitus, dyslipidemia and associated medications: statins, metformin, and aspirin. The primary endpoints of our study were incidence of lung cancer (ICD-9-CM codes 162.X) in COPD patients during the influenza season, non-influenza season (April-September), and all seasons during the follow-up years.

### 2.1. Statistical analysis

A propensity scores (PS) are used to reduce selection bias and estimate effect of vaccination by accounting for the covariates that predict receiving the intervention (vaccine) with a logistic regression model.<sup>[10]</sup> Categorical variables were compared using chi-square test and continuous variables using  $t$  test. The hazard ratio (HR) and 95% confidence interval (CI) for the association between the influenza vaccination and the occurrence of lung

cancer in COPD patients was analyzed by Cox proportional hazards regression analysis. The association between the seasonal effect of vaccination and incidence of lung cancer was also examined. To study the dose-effect of influenza vaccinations on incidence of lung cancer, we categorized the patients into four groups by vaccination status (unvaccinated, total number of vaccinations: 1, 2 to 3, and  $\geq 4$ ). These data were stratified according to the patients' age, sex, comorbidity, and associated medication use. Sensitivity analyses were applied to evaluate the difference and consistency between the influenza vaccination use and the risk of lung cancer in COPD patients. This study performed all statistical analyses using SPSS 19.0 and SAS 9.2 software. The significance criterion was set at  $P < .05$ .

### 3. Results

Totally, 28,752 eligible individuals were enrolled into the COPD cohort. Of the study population, 51% (14,630) received influenza vaccination; the rest (49%) of the COPD patients did not receive influenza vaccination (Table 1). There was a significant difference ( $P < .001$ ) between the two groups including distributions of age, level of urbanization, and monthly income (Table 1). Table 1 also showed prevalence of certain preexisting medical comorbidities, including CCI ( $P < .001$ ), diabetes ( $P = .005$ ), hypertension ( $P < .001$ ) and dyslipidemia ( $P < .001$ ) was higher in the unvaccinated than vaccinated group. In addition, the unvaccinated group demonstrated higher percentage of

**Table 1**  
Characteristic of the COPD cohort study patients.

	Whole cohort (n=28,752)		Unvaccinated (n=14,122)		Vaccinated (n=14,630)		P*
	n	%	n	%	n	%	
Age, years (Mean $\pm$ SD)	69.62 (9.26)		67.91 (10.20)		71.27 (7.89)		<.001
55–64	10,463	36.39	6927	49.05	3356	24.17	<.001
65–74	9899	34.43	3495	24.75	6404	43.77	
$\geq 75$	8390	29.18	3700	24.75	4690	32.06	
Gender							
Female	12,741	44.31	6247	44.24	6494	44.39	.795
Male	16,011	55.69	7875	55.76	8136	55.61	
CCI Index†							
0	6074	21.13	2879	20.39	3195	21.84	<.001
1	7722	26.86	3674	26.02	4048	27.67	
2	6222	21.64	3081	21.82	3141	21.47	
$\geq 3$	8734	30.38	4488	31.78	4246	29.02	
Diabetes							
No	20,141	70.05	9784	69.28	10357	70.79	.005
Yes	8611	29.95	4338	30.72	4273	29.21	
Hypertension							
No	10,939	38.05	5362	39.88	5307	36.27	<.001
Yes	17,813	61.95	8490	60.12	9323	63.73	
Dyslipidemia							
No	18,921	65.81	9302	63.96	9889	67.59	<.001
Yes	9831	34.19	5090	36.04	4741	32.41	
Statin							
<28 d	20,452	71.13	10,652	75.43	9800	66.99	<.001
28–365 d	4067	14.15	1783	12.63	2284	15.61	
>365 d	4233	14.72	1687	11.95	2546	17.40	
Metformin							
<28 d	22,513	78.30	11,350	80.37	11163	76.30	<.001
28–365 d	2116	7.36	1080	7.65	1036	7.08	
>365 d	4123	14.34	1692	11.98	2431	16.62	
Aspirin							
<28 d	16,037	55.78	9259	65.56	6778	46.33	<.001
28–365 d	5824	20.26	2503	17.72	3321	22.70	
>365 d	6891	23.97	2360	16.71	4531	30.97	
Level of urbanization							
Urban	19,100	66.46	10031	71.03	9079	62.06	<.001
Suburban	6297	21.90	2801	19.83	3496	23.90	
Rural	3345	11.63	1290	9.13	2055	14.05	
Monthly income (NT\$)							
0	3066	10.66	1329	9.41	1737	11.87	<.001
1–21,000	7378	25.66	3106	21.99	4272	29.20	
21,000–33,300	10,680	37.15	4809	34.05	5871	40.13	
$\geq 33,301$	7628	26.53	4878	34.54	2750	18.80	

COPD = chronic obstructive pulmonary disease, SD = Standard Deviation.

\* Comparison between Unvaccinated and Vaccinated.

† CCI Index: Charlson Comorbidity Index.

**Table 2**  
**Risk of lung cancer among unvaccinated and vaccinated in study cohort.**

All group (n = 28,752)	Unvaccinated (total follow-up 62,471.2 person years)		Vaccinated (total follow-up 10,6461.4 person-years)		Adjusted HR <sup>¶</sup> (95% C.I.)
	No. of patients with cancer	Incidence rate (per 10 person-years) (95% C.I.)	No. of patients with cancer	Incidence rate (per 10 person-years) (95% C.I.)	
Whole cohort					
Influenza season	329	526.6 (469.7, 583.6)	258	242.3 (212.8, 271.9)	0.38 (0.32, 0.45) <sup>***</sup>
Non-influenza season	292	467.4 (413.8, 521.0)	243	228.3 (199.6, 257.0)	0.42 (0.35, 0.51) <sup>***</sup>
All season	621	994.1 (915.9, 1072.2)	501	470.6 (429.4, 511.8)	0.40 (0.35, 0.45) <sup>***</sup>
Age, 55–64 <sup>*</sup>					
Influenza season	112	303.4 (247.2, 359.6)	35	112.8 (75.4, 150.2)	0.34 (0.26, 0.44) <sup>***</sup>
Non-influenza season	118	319.6 (262.0, 377.3)	33	106.4 (70.1, 142.6)	0.36 (0.24, 0.53) <sup>***</sup>
All season	230	623.0 (542.5, 703.5)	68	219.1 (167.1, 271.2)	0.37 (0.28, 0.49) <sup>***</sup>
Age, 65–74 <sup>†</sup>					
Influenza season	120	811.5 (666.3, 956.7)	131	273.2 (226.5, 320.0)	0.34 (0.26, 0.44) <sup>***</sup>
Non-influenza season	79	534.2 (416.4, 652.0)	113	235.7 (192.2, 279.2)	0.45 (0.33, 0.60) <sup>***</sup>
All season	199	1354.7 (1158.7, 1532.7)	244	508.9 (445.1, 572.8)	0.38 (0.32, 0.46) <sup>***</sup>
Age, ≥75 <sup>‡</sup>					
Influenza season	97	901.1 (721.7, 1080.4)	92	334.7 (266.3, 403.1)	0.39 (0.29, 0.52) <sup>***</sup>
Non-influenza season	95	882.5 (705.0, 1059.9)	97	352.9 (282.6, 423.1)	0.39 (0.29, 0.52) <sup>***</sup>
All season	192	1783.5 (1531.3, 2035.8)	189	687.5 (589.5, 785.6)	0.39 (0.32, 0.48) <sup>***</sup>
Female <sup>§</sup>					
Influenza season	101	338.6 (272.5, 404.6)	71	145.4 (111.5, 179.2)	0.38 (0.28, 0.52) <sup>***</sup>
Non-influenza season	89	298.3 (236.4, 360.3)	76	155.6 (120.6, 190.6)	0.51 (0.37, 0.70) <sup>***</sup>
All season	190	636.9 (546.4, 727.5)	147	300.9 (252.3, 349.6)	0.44 (0.35, 0.55) <sup>***</sup>
Male <sup>  </sup>					
Influenza season	228	698.5 (607.9, 789.2)	187	342.6 (278.1, 371.1)	0.36 (0.30, 0.45) <sup>***</sup>
Non-influenza season	203	621.9 (536.4, 707.5)	167	289.9 (245.9, 333.8)	0.38 (0.31, 0.47) <sup>***</sup>
All season	431	1320.5 (1195.8, 1445.1)	354	614.4 (550.4, 678.4)	0.37 (0.32, 0.43) <sup>***</sup>

C.I. = confidence interval, HR = hazard ratio.

<sup>\*\*\*</sup>  $P < .001$ .

<sup>\*</sup> Total follow-up 36,918.2 person-year for unvaccinated and 31,029.5 for vaccinated.

<sup>†</sup> Total follow-up 14,787.9 person-year for unvaccinated and 47,942.2 for vaccinated.

<sup>‡</sup> Total follow-up 10,765.1 person-year for unvaccinated and 27,489.7 for vaccinated.

<sup>§</sup> Total follow-up 29,831.1 person-year for unvaccinated and 48,847.2 for vaccinated.

<sup>||</sup> Total follow-up 32,640.1 person-year for unvaccinated and 57,614.3 for vaccinated.

<sup>¶</sup> Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, level of urbanization, Monthly income in propensity score.

comorbidities-associated medication use including metformin ( $P < .001$ ), statin ( $P < .001$ ) and aspirin ( $P < .001$ ) than in vaccinated group did.

The incidence of the lung cancer was significantly lower in the influenza vaccinated group after we adjusted for potential confounders (adjusted HR 0.40, 95% CI 0.35–0.45  $P < .001$ ) than in the unvaccinated group (Table 2). The similar protective effects were also observed in both sexes and all elderly-age groups (55–64 years, 65–74 years, and 75 years and older) irrespective of influenza seasonality (Table 2).

### 3.1. Sensitivity analysis

The sensitivity analysis adjustments had an effect on evaluation of the association of influenza vaccination use with risk of lung cancer in different models. Table 3 demonstrates that the protective effects in the influenza vaccinated patients when stratified according to the total number of vaccinations in the main model and remained significant effect in subgroup analysis. Interestingly, dose-dependent protective effect can be seen when patients received influenza vaccination more than two doses (Table 3). The adjusted HRs for lung cancer risk were 0.48 (0.40–0.54) and 0.24 (0.20–0.29) for patients who received 2 to 3 and ≥4 vaccinations during the follow-up period.

## 4. Discussion

We observed that patients with COPD who had received influenza vaccination could reduce risk of lung cancer in this population-based cohort study. In our study, the mean age of patients received influenza vaccination was older than unvaccinated group and significant difference in comorbidity with related medications between the 2 groups was found. These different factors could influence the risk of lung cancer development in general patients including age, statin and metformin use. COPD patients are at increased risk for development of primary lung cancer,<sup>[11]</sup> particularly for squamous cell carcinoma.<sup>[12]</sup> The association between COPD and lung cancer is attributed from shared smoking exposure and subsequent airflow limitation,<sup>[13]</sup> whereas some studies demonstrated the risk of both diseases independent of patient age or extent of tobacco use.<sup>[2,3]</sup> The possible mechanisms in connection of COPD and lung cancer are oxidative stress and chronic inflammation.<sup>[14,15]</sup>

First, the most common cause of COPD is cigarettes smoking which introduce particulates and oxidant including reactive nitrogen and oxygen species (RNOS)<sup>[16]</sup> into airways and lung parenchyma. The RNOS subsequently resulted in oxidative stress and injury of epithelial cells lining on airways and alveolar walls.

**Table 3**  
**Sensitivity analysis of adjusted HRs of vaccination in risk reduction of lung cancer.**

	Unvaccinated Adjust HR (95% C.I.)	Vaccinated			P for trend
		1 Adjust HR (95% C.I.)	2-3 Adjust HR (95% C.I.)	≥4 Adjust HR (95% C.I.)	
Main model <sup>‡</sup>	1.00	0.65 (0.55,0.77)***	0.48 (0.40,0.54)***	0.24 (0.20,0.29)***	<.001
Additional covariates <sup>§</sup>					
Main model+statin	1.00	0.66 (0.56,0.79)***	0.48 (0.40,0.56)***	0.24 (0.20,0.29)***	<.001
Main model+metformin	1.00	0.65 (0.55,0.77)***	0.46 (0.39,0.55)***	0.23 (0.19,0.28)***	<.001
Main model+RAA	1.00	0.69 (0.59,0.82)***	0.51 (0.43,0.60)***	0.26 (0.21,0.32)***	<.001
Main model+aspirin	1.00	0.69 (0.58,0.81)***	0.50 (0.42,0.59)***	0.25 (0.21,0.31)***	<.001
Subgroup effects					
Age, years					
55–64	1.00	0.51 (0.34,0.75)***	0.40 (0.27,0.60)***	0.21 (0.12,0.36)***	<.001
65–74	1.00	0.76 (0.59,0.97)***	0.46 (0.36,0.60)***	0.21 (0.16,0.28)***	<.001
≥75	1.00	0.58 (0.44,0.77)***	0.44 (0.34,0.58)***	0.23 (0.17,0.32)***	<.001
Sex					
Female	1.00	0.74 (0.55,1.00)*	0.53 (0.40,0.72)***	0.21 (0.14,0.31)***	<.001
Male	1.00	0.61 (0.50,0.75)***	0.42 (0.34,0.51)***	0.22 (0.17,0.27)***	<.001
CCI Index <sup>†</sup>					
0	1.00	0.57 (0.40,0.80)**	0.41 (0.30,0.58)***	0.18 (0.12,0.27)***	<.001
1	1.00	0.64 (0.46,0.88)**	0.58 (0.43,0.78)***	0.24 (0.17,0.33)***	<.001
2	1.00	0.68 (0.48,0.96)*	0.46 (0.32,0.66)***	0.19 (0.12,0.30)***	<.001
≥3	1.00	0.72 (0.52,1.01)	0.35 (0.24,0.52)***	0.28 (0.19,0.41)***	<.001
Diabetes					
No	1.00	0.68 (0.56,0.83)***	0.46 (0.38,0.56)***	0.23 (0.19,0.29)***	<.001
Yes	1.00	0.57 (0.40,0.80)**	0.42 (0.32,0.62)***	0.20 (0.13,0.30)***	<.001
Dyslipidemia					
No	1.00	0.68 (0.56,0.83)***	0.48 (0.39,0.58)***	0.25 (0.20,0.31)***	<.001
Yes	1.00	0.58 (0.42,0.80)***	0.42 (0.30,0.57)***	0.15 (0.10,0.23)***	<.001
Hypertension					
No	1.00	0.57 (0.44,0.74)***	0.46 (0.36,0.59)***	0.19 (0.14,0.26)***	<.001
Yes	1.00	0.72 (0.58,0.90)**	0.46 (0.37,0.58)***	0.25 (0.19,0.32)***	<.001
Statin					
<28 d	1.00	0.63 (0.52,0.76)***	0.42 (0.35,0.51)***	0.23 (0.19,0.29)***	<.001
28–365 d	1.00	1.08 (0.65,1.79)	0.69 (0.42,1.14)	0.31 (0.17,0.56)***	<.001
>365 d	1.00	0.68 (0.31,1.52)	1.21 (0.68,2.16)	0.35 (0.18,0.69)**	.013
Metformin					
<28 d	1.00	0.66 (0.55,0.76)***	0.43 (0.36,0.52)***	0.20 (0.16,0.25)***	<.001
28–365 d	1.00	0.72 (0.35,1.47)	0.58 (0.29,1.17)	0.45 (0.23,0.92)*	.019
>365 d	1.00	0.61 (0.30,1.24)	0.90 (0.52,1.54)	0.40 (0.22,0.72)**	.008
Aspirin					
<28 d	1.00	0.69 (0.56,0.85)***	0.43 (0.34,0.53)***	0.22 (0.16,0.28)***	<.001
28–365 d	1.00	0.69 (0.47,1.01)	0.53 (0.37,0.78)***	0.30 (0.20,0.45)***	<.001
>365 d	1.00	0.95 (0.58, 1.57)	1.03 (0.68,1.56)	0.44 (0.28,0.69)***	.001

HR=hazard ratio.

\* P<.05.

\*\* P<.01.

\*\*\* P<.001.

† CCI index: Charlson Comorbidity Index.

‡ Main model is adjusted for age, sex, Charlson comorbidity index, diabetes, hypertension, dyslipidemia, level of urbanization, Monthly income in propensity score.

§ The models were adjusted for covariates in the main model as well as each additional listed covariate.

The oxidative stress induced the accumulation of cell injury by DNA damage, lipid peroxidation, oxidation of amino acids, and oxidation of inorganic enzyme co-factors.<sup>[15,17]</sup> In addition, unbalanced oxidant-induced deoxyribonucleic acid (DNA) damage and repair in COPD triggered to develop lung cancer,<sup>[18]</sup> involving cancer initiation,<sup>[19]</sup> and progression.<sup>[20]</sup>

Second, COPD is characterized by chronic inflammation of lower airways, which macrophages, neutrophils, and lymphocytes are main immune cells orchestrated and amplified the inflammation in the progression of disease.<sup>[4]</sup> The propagation and the maintenance of inflammation increased risk of cancer development was reported in the literature,<sup>[21]</sup> but the link

between chronic low airways inflammation to lung cancer is still not fully elucidated.<sup>[22]</sup> Different phenotype of immune cells infiltration in the lung were found between COPD and lung cancer. Macrophages, T helper 1 (T<sub>H</sub>1) or cytotoxic profile are predominant inflammatory cells in COPD,<sup>[23]</sup> however, most solid tumors polarize immune cells towards a M2 macrophages and T helper 2 (T<sub>H</sub>2) lymphocyte.<sup>[24]</sup> The time-varying on phenotype of immune cells profile in COPD lead to lung cancer development.<sup>[25]</sup> These changes may be attributed from that oxidative stress in COPD patients provide genotoxicity for DNA adduct formation with subsequent genetic mutation,<sup>[26]</sup> which triggers early stage neoplasm forming and secreting cytokines and

chemokines that skew the immune cell profiles in favor of tumor promotion.<sup>[27]</sup>

Exploring possible pathogenesis of linking COPD to lung cancer mentioned above, we could provide specific strategies for COPD patients to reduce risk of lung cancer. Chronic anti-oxidant therapy, for example N-acetyl cysteine (NAC) may be benefit of reducing exacerbations of COPD and lung cancer incidence based of mitigating oxidative stress in both diseases but the results from trials of NAC treatment in COPD showed small reduction in acute exacerbations,<sup>[28]</sup> furthermore, use of antioxidants in mice increased cancer risk in COPD model.<sup>[29]</sup> Given shared mechanism of chronic inflammation in both diseases, long-term treatment with anti-inflammatory agent of inhaled corticosteroid (ICS) in COPD was performed but the results showed controversial in survival benefit of lung cancer.<sup>[30,31]</sup> Changes over time of lipid metabolism in cancers including lung cancer has been investigated before but the protective effect of statin administering was not clearly demonstrated by those studies.<sup>[32,33]</sup>

Vaccination in preventing cancer has been made significant progress particularly in hepatocellular carcinoma with hepatitis B (HBV) vaccine and HPV-related cervical and other cancers with HPV vaccines.<sup>[34]</sup> Not any research has been reported before about vaccination in lung cancer prevention. This is the first population-based cohort study to show influenza vaccination could reduce lung cancer in COPD patients. The possible explanation for the promising result may be decreasing frequency of exacerbations in patients of COPD caused by influenza virus infection with resultant persistence of inflammation. Another possible reason is annual influenza vaccination administering may trigger T<sub>H</sub>1 immune response to augment anti-tumor defense. In addition, the dose-dependent effect showed in our study implicated the boosted and consolidated anti-tumor immunity after repeated receiving influenza vaccination.

Our group analyzed the associated of influenza vaccination in COPD with the reduction of hospitalization for acute coronary syndrome from the same database,<sup>[35]</sup> which suggested the protective effect of influenza vaccination on endothelial cells of COPD patients. In this study, we showed the influence of influenza vaccination on reduction of lung cancer in COPD, which may implied the similar protective role on epithelial cells of lung in patients. However, some limitations of this study should be addressed. First, several confounding factors relevant to cancers, including smoking, alcohol intake, and other over-the-counter drug use, body mass index, were not contained in our database. Second, the diagnoses of COPD and the vaccination status in our study were according to ICD-9 codes or drug codes, thus the diagnostic accuracy of the database may be a problem. Finally, we presumed all prescribed medications associated with anti-cancers such as statin and metformin were actually taken by patients to mitigate the effect of noncompliance to influence our result.

## 5. Conclusion

In conclusion, this study is the first article to demonstrate the protective effect of influenza vaccination against lung cancer in COPD patients. Furthermore, this study showed dose-dependent effect in reducing the incidence of lung cancer. In the future, there is need for prospective large clinical trials and elucidation underlying mechanisms in basis of this study.

## Author contributions

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