International Journal of Infectious Diseases 88 (2019) 8–13

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Association between the risk of lung cancer and influenza: A population-based nested case-control study

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ARTICLE INFO

Article history:
Received 3 May 2019
Received in revised form 24 July 2019
Accepted 24 July 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Influenza
Lung cancer
Nested case-control study
Taiwan Cancer Registry Database

ABSTRACT

Background: Previous animal studies have shown that certain respiratory oncoviruses can lead to tumorigenesis, especially influenza virus. However, no clinical studies other than animal studies have been conducted to test this hypothesis.
Objective: To investigate the association between influenza and the risk of lung cancer using the Taiwan Cancer Registry Database (TCRD) and Taiwan's National Health Insurance Research Database (NHIRD).
Methods: We identified a study cohort consisting of patients aged 40 years or above who were enrolled in the NHIRD between 1 January 2012 and 31 December 2014. Among them, we identified patients with lung cancer (cases) and their matched controls (matched by age, sex, and disease risk score (DRS) at a ratio of 1:10). Multivariate conditional logistic regression models were used to evaluate the association between exposure to influenza (timing and cumulative number) and risk of lung cancer.
Results: We identified 32,063 cases and 320,627 matched controls. Influenza was associated with a 1.09-fold increased risk of lung cancer (aOR 1.09, 95% CI 1.04–1.14, $p < 0.0001$). The risk of lung cancer increased slightly with cumulative exposure to influenza (1–2 exposures: aOR 1.05, 95% CI 1.00–1.11; 3-4 exposures: aOR 1.12, 95% CI 1.00–1.25; 5+ exposures: aOR 1.25, 95% CI 1.13–1.39).
Conclusion: Exposure to influenza was associated with an increased risk of lung cancer and the risk increased with cumulative exposure to influenza. However, the lack of valid information on smoking could lead to confounding, and future studies collecting patients' smoking histories are warranted to validate the association between influenza and lung cancer.

Introduction

Lung cancer has become the leading cause of cancer-related mortality in recent decades, not only worldwide but also in Taiwan (Torre et al., 2015; Wang et al., 2013). The average 5-year survival rates have been reported to be less than 30% for patients who are potentially operable and from 6% to 18% for those who have locally advanced lesions (Ferlay et al., 2015). New strategies and therapy for lung cancer have been developed in recent years which have improved patient progression-free survival (e.g., tyrosine kinase inhibitors) (Herbst et al., 2018). Nevertheless, available treatment options have not significantly prolonged overall survival of lung cancer. The prevention and early detection of lung cancer is thus critical to avoid tumorigenesis and eradicate malignant tumors, and ultimately to decrease mortality from lung cancer.

Environmental risk factors, particularly tobacco smoke, have been proven to be risk factors for lung cancer in Western countries.

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https://doi.org/10.1016/j.ijid.2019.07.030

However, around 25% of lung cancers occur in never-smokers (Cheng et al., 2016; Planchard and Besse, 2015). Moreover, the incidence of lung cancer among never-smokers has increased, especially in Asian women, in whom more than 50% of cases occur in never-smokers (Toh et al., 2004). This indicates the urgent need to explore other pathological mechanisms for tumor growth and malignant transformation in this patient population.

Chronic inflammation has been postulated to participate in tumor growth and malignant transformation (Philip et al., 2004; Klein and Klein, 1985). In addition to well-known environmental risk factors such as tobacco smoke, viruses have been reported to be associated with cancer formation. The so-called oncoviruses may have direct and indirect oncogenic effects by activating inflammatory signaling pathways and cytokines (Read and Douglas, 2014).

Among all viruses associated with inflammatory signaling pathways and cytokines of the lower respiratory system, influenza viruses are especially important in terms of their potential link to lung cancer. Influenza occurs worldwide in seasonal or yearly outbreaks, resulting in three to five million cases of severe illness and around 250 thousand to 500 thousand deaths (Stöhr, 2002). Previous animal studies have shown that certain respiratory oncoviruses can lead to tumorigenesis, especially influenza virus (Baskerville et al., 1974; Kotin and Wiseley, 1963; Shimkin and Stoner, 1975). However, no clinical studies other than animal studies have been conducted to test this hypothesis.

The aim of this study was, therefore, to test the hypothesis of an association between influenza virus infection and the risk of lung cancer using the Taiwan Cancer Registry Database (TCRD) and Taiwan's National Health Insurance Research Database (NHIRD).

Materials and methods

Study design and data source

In this nested case-control study, we enrolled patients aged older than 40 years who were registered in the TCRD and NHIRD. The TCRD is funded by the Ministry of Health and Welfare (MOHW), Taiwan and was established in 1979. It is considered to be an informative nationwide database for cancer surveillance with 98.4% completeness and 91.5% morphological verification regarding a cancer diagnosis according to the data in 2012 (Chiang et al., 2016; Chiang et al., 2015). The NHIRD is a nationwide database containing the claims data of all beneficiaries enrolled in the National Health Insurance (NHI) program in Taiwan. The NHI program was launched in 1995 and covers over 99% of the population in Taiwan (23.58 million in 2018). The NHIRD is comprised of detailed healthcare information on demographics and healthcare utilization, including outpatient visits, hospital admissions, and prescription medications (Hsiao et al., 2007; Hsing and Ioannidis, 2015).

Ethical statement

The identification numbers of the beneficiaries were encrypted to ensure their confidentiality. However, unique identification numbers allowed for interconnections among all database subsets of the NHI program. The protocol of this study was approved by the Research Ethics Committee of National Taiwan University Hospital (registration number, 201604051W).

Study population

The patient cohort consisted of patients aged 40 years or above who were enrolled in the NHIRD between 1 January 2012 and 31 December 2014. The cohort entry date was defined as the first date of the first record in the NHIRD from 2012-2014. The inclusion criteria were patients aged 40 years or older, and with claims records for a continuous period of at least 12 months prior to the cohort entry date, which enabled us to collect baseline characteristics. Patients with any cancer diagnosis prior to 1 January 2012 were excluded so that our study cohort was comprised of cancer-naïve patients. The enrollment flowchart for this study is shown in Figure 1.

Cases and controls

We defined cases as patients who were diagnosed with lung cancer in the TCRD during the study period (International Classification of Diseases for Oncology, Third edition (ICD-O-3) codes (Fritz et al., 2013) C33.9, C34.0–C34.9). The positive predictive value of identifying lung cancer by diagnosis code has been reported to be 51.1%–99.4% (Ramsey et al., 2009). The diagnosis date of lung cancer was defined as the index date. Through risk set sampling, we randomly selected up to ten controls for each case in the original cohort matched by age (±5 years), sex, and the disease risk score (DRS, ±0.01). In this study, DRS was defined as the probability of the cohort developing lung cancer, and was estimated by fitting covariates of the patients' underlying diseases, including tuberculosis [International Classification of Diseases, Ninth edition, Clinical Modification (ICD-9-CM) codes 010-018], pneumonia (ICD-9-CM codes 480–486), bronchiectasis (ICD-9-CM code 494), pneumoconiosis (ICD-9-CM codes 500–505), pulmonary alveolar pneumonopathy (ICD-9-CM code 516), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), and asthma (ICD-9-CM code 493), into a multivariate logistic regression model (Desai et al., 2016).

Exposure to influenza

The exposure of interest in this study was influenza, defined as a diagnosis of influenza (ICD-9-CM code 487) or the use of oseltamivir or zanamivir. As an influenza diagnosis that occurred too close to the index date (diagnosis of lung cancer) may be pre-symptoms associated with lung cancer, we specifically excluded influenza diagnoses that occurred within 3 months before the index date (−1∼ −3 months). We further categorized exposure into recent exposure (−4∼ −12 months) and former exposure (−13 ∼ −36 months) based on the "latest" diagnosis or prescription date prior to the index date. In addition, to evaluate the influence of different definitions of exposure, sensitivity analyses were conducted: (1) excluded influenza diagnosis that occurred within 6 months before index date (−1∼ −6 months) or/and (2) categorized recent and former exposure based on the "earliest" diagnosis or prescription date prior to the index date. We also counted episodes of exposure and defined an episode of influenza as one diagnosis of influenza or ever having used oseltamivir or zanamivir in an admission or outpatient visit.

Statistical and subgroup analyses

Paired t-tests were used to compare variables between cases and controls for continuous variables, and McNemar's test was used for categorical variables. We used multivariate conditional logistic regression models to estimate the association between influenza and lung cancer. To further control for potential confounding factors, all models were adjusted for Charlson comorbidity index (CCI; grouped as 0, 1–2, and 3+) and co-morbidities that might be associated with lung cancer, including tuberculosis, pneumonia, bronchiectasis, pneumoconiosis, pulmonary alveolar pneumonopathy, chronic obstructive pulmonary disease, and asthma. Furthermore, we performed subgroup analyses by sex and age (40–64 years old versus 65 years

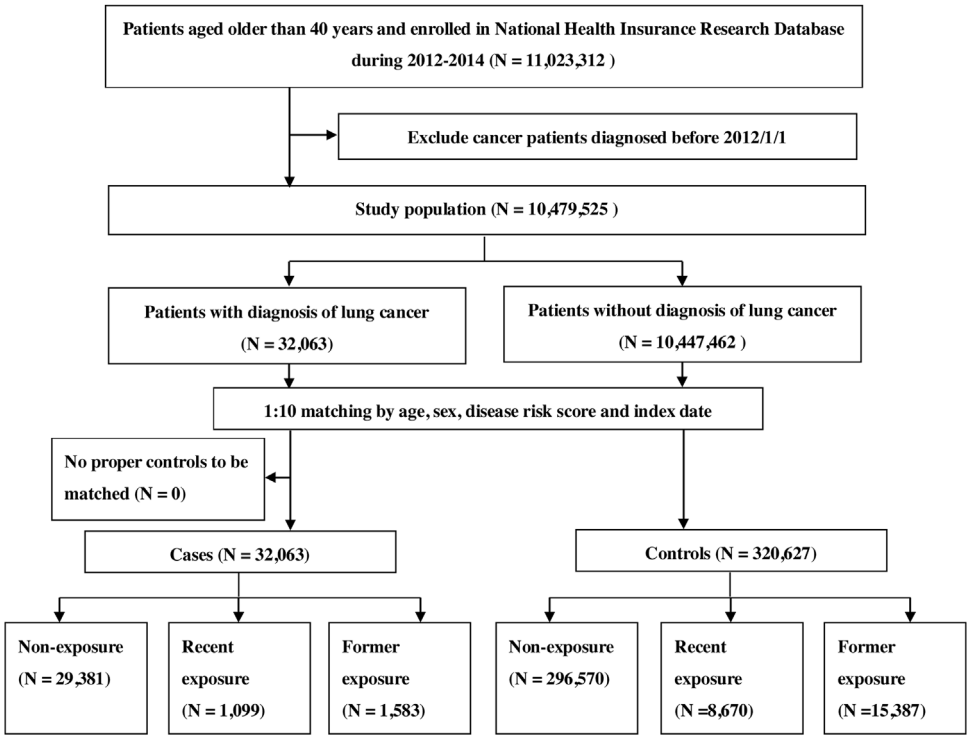

Figure 1. Flow chart of the study population.
Inclusion and exclusion criteria for the study cohort and selection process for the cases and the controls.

and above) to evaluate whether the association between influenza and the risk of lung cancer differed by sex and age. Both crude odds ratios (cORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were presented. All statistical tests were two-sided, and the significance level was set at 0.05. All data in this study were analyzed using SAS® software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

The study cohort consisted of 10,479,525 cancer-naïve patients. During the follow-up period, we identified 32,063 cases and 320,627 controls matched by age, sex, and DRS. The mean age was 67.4 years, and 60.3% of the patients were male. As demonstrated in Table 1, age and sex are both well balanced between the cases and controls. There were significant differences in covariates including CCI and respiratory co-morbidities between the cases and controls, for which statistical adjustments were performed.

As shown in Table 2, exposure to influenza was associated with a 1.09-fold increased risk of lung cancer (aOR 1.09, 95% CI 1.04–1.14, $p < 0.0001$). Among the patients with recent exposure to influenza, there was a 22% increased risk of lung cancer (aOR 1.22, 95% CI 1.14–1.30); whereas the association was not statistically significant in the patients with former exposure to influenza (aOR 1.01, 95% CI 0.96–1.07). In contrast to primary analysis (using the "latest" diagnosis or prescription date to define the exposure status), sensitivity analyses (using the "earliest" diagnosis or prescription date to define the exposure status) showed that the number of

Table 1
Baseline characteristics of lung cancer cases and their matched controls.

Variable		Case (N = 32,063)		Control (N = 320,627)		Univariate OR		
		N	(%)	N	(%)	OR	95 % CI	*p*-Value
Gender	Male	19336	(60.3)	193357	(60.3)			–
	Female	12727	(39.7)	127270	(39.7)			
Age (years)	Mean (SD)	67.4	(12.3)	67.3	(12.4)			–
	Median (Q1,Q3)	68	(58,77)	68	(58,77)			
Age	40–64	13565	(42.3)	135650	(42.3)			–
	65+	18498	(57.7)	184977	(57.7)			
Charlson comorbidity index	0	17425	(54.3)	186875	(58.3)	ref		<0.0001
	1-2	11482	(35.8)	105326	(32.9)	1.19	1.16–1.23	
	3 and above	3156	(9.8)	28426	(8.9)	1.23	1.18–1.28	
Tuberculosis		315	(1.0)	1351	(0.4)	2.43	2.14–2.75	<0.0001
Pneumonia		1598	(5.0)	9424	(2.9)	1.81	1.71–1.92	<0.0001
Bronchiectasis		252	(0.8)	1670	(0.5)	1.53	1.33–1.75	<0.0001
Pneumoconiosis		66	(0.2)	559	(0.2)	1.19	0.92–1.55	0.1931
Pulmonary alveolar pneumonopathy		23	(0.1)	79	(0.0)	2.96	1.85–4.73	<0.0001
Chronic Obstructive Pulmonary Disease		3054	(9.5)	18100	(5.6)	2.04	1.95–2.14	<0.0001
Asthma		1431	(4.5)	9062	(2.8)	1.66	1.56–1.76	<0.0001

*Odds ratio and p-value were estimated by fitting conditional logistic model. Gender and age are matching variable and not fitted.

Table 2
Unadjusted and adjusted odds ratios for lung cancer and exposure to influenza.

		Case (N = 32,063)		Control (N = 320,627)		Crude OR			Adjusted OR		
		N	(%)	N	(%)	OR	95 % CI	*p*-Value	OR	95 % CI	*p*-Value
Influenza	Non-exposure	29381	(91.6)	296570	(92.5)	ref		<0.0001	ref		<0.0001
	exposure	2682	(8.4)	24057	(7.5)	1.13	1.08–1.17		1.09	1.04–1.14	
Timing of exposure to influenza	Non-exposure	29381	(91.6)	296570	(92.5)	ref		<0.0001	ref		<0.0001
	Recent exposure	1099	(3.4)	8670	(2.7)	1.28	1.20–1.36		1.22	1.14–1.30	
	Former exposure	1583	(4.9)	15387	(4.8)	1.04	0.98–1.10		1.01	0.96–1.07	
Counts of influenza episodes –. (%)	Non-exposure	29381	(91.6)	296570	(92.5)	ref		<0.0001	ref		<0.0001
	1–2	1931	(6.0)	17883	(5.6)	1.09	1.04–1.14		1.05	1.00–1.11	
	3–4	351	(1.1)	3074	(1.0)	1.15	1.03–1.29		1.12	1.00–1.25	
	5+	400	(1.2)	3100	(1.0)	1.30	1.17–1.45		1.25	1.13–1.39	

patients categorized as former exposure increased and the association between former exposure and lung cancer became significant (aOR 1.06, 95% CI 1.02–1.12) (Supplementary Table S1).

The risk of lung cancer increased with cumulative episodes of influenza. The aORs of risk of lung cancer were 1.05 (95% CI 1.00–1.11), 1.02 (95% CI 1.13–1.39) and 1.25 (95% CI 1.13–1.39) in the patients with 1–2, 3–4 and 5+ episodes of influenza infection, respectively (Table 3).

The association between influenza and the risk of lung cancer persisted irrespective of sex and age as indicated in Tables 4 and 5. Overall, there was no significant difference in the association between influenza and the risk of lung cancer between the male and female patients. However, the risk of lung cancer associated with recent exposure to influenza was slightly higher in men than in women (men: aOR 1.24, 95% CI 1.14–1.35 versus women: aOR 1.18, 95% CI 1.07–1.31). Similarly, the association between more episodes of influenza and the risk of lung cancer was stronger in the male patients, with a 1.37-fold increased risk of lung cancer in the male patients with 5+ episodes of influenza (aOR 1.37, 95% CI 1.20–1.56), whereas there was no significant association in the female patients.

With regards to differences in age, patients aged 40–64 years with recent exposure to influenza tended to have a higher risk of lung cancer than those aged 65 years and above (40–64 years old: aOR 1.32, 95% CI 1.20–1.46 versus 65 years and older: aOR 1.14, 95% CI 1.05–1.24). A dose-response relationship between the number of influenza episodes and the risk of lung cancer was observed in both age groups, particularly in patients aged 40–64 years. Patients aged 40-64 years with 5+ episodes of influenza were associated with a 1.35-fold increased risk of lung cancer (aOR 1.35, 95% CI 1.14–1.60), while the aOR was 1.19 (95% CI 1.04–1.36) in patients aged 65 years and older.

Table 3
Adjusted odds ratio for lung cancer and counts of exposure to influenza.

Variable	Adjusted OR	95 % CI	*p*-Value
Influenza			<0.0001
Non-exposure	ref		
1-2	1.05	1.00–1.11	
3-4	1.12	1.00–1.25	
5+	1.25	1.13–1.39	
Charlson comorbidity index			<0.0001
0	ref		
1-2	1.08	1.05–1.10	
3 and above	1.01	0.97–1.06	
Tuberculosis	2.01	1.76–2.28	<0.0001
Pneumonia	1.45	1.37–1.54	<0.0001
Bronchiectasis	1.08	0.94–1.24	0.2753
Pneumoconiosis	1.04	0.80–1.36	0.7580
Pulmonary alveolar pneumonopathy	2.43	1.51–3.92	0.0003
Chronic Obstructive Pulmonary Disease	1.80	1.71–1.89	<0.0001
Asthma	1.41	1.33–1.50	<0.0001

Discussion

To the best of our knowledge, this population-based nested case-control study is the first to test the hypothesis that influenza is associated with the risk of lung cancer in a real-world setting. We found that influenza was associated with a 1.09-fold increased risk of lung cancer, and that the risk increased with cumulative exposure to influenza, with a 25% increased risk of lung cancer observed in patients with 5+ episodes of influenza infection. Our findings thus provide "real-world evidence" to support the potential link between influenza virus infection and lung malignant transformation observed in animal studies (Baskerville et al., 1974; Kotin and Wiseley, 1963; Shimkin and Stoner, 1975).

Our study thus has important implications for public health, particularly given the urgent need to identify the mechanisms responsible for tumor growth and malignant transformation in lung cancer. Our findings suggest that influenza infection is a potential risk factor for lung cancer. The mechanism of inflammation attributed to infection may be an explanation for the potential link, as suggested in other studies involving oncogenic viruses. For example, the Jaagsiekte sheep retrovirus has been shown to cause pulmonary adenomatosis in sheep, and it has been proposed to resemble human bronchioloalveolar carcinoma, although the evidence of oncogenic viruses in lung cancer is still controversial (Mornex et al., 2003). Moreover, human papillomavirus (HPV), Epstein-Barr virus, BK virus, JC virus, human cytomegalovirus (CMV), simian virus, and measles virus have all been reported to be possible causes of lung cancer, although the results remain inconclusive (Brouchet et al., 2005; Castro et al., 2001; Giuliani et al., 2007; Rezazadeh et al., 2009; Sion-Vardy et al., 2009). Pneumonia, and especially Chlamydia pneumonia infection, has been postulated to be involved in lung cancer carcinogenesis (Chaturvedi et al., 2010), and pulmonary tuberculosis has also been reported to be a potent risk factor for lung cancer (Yu et al., 2011).

In addition, various kinds of microbiological agents and inorganic environmental air pollutants have been reported to be important risk factors for lung cancer (Hosgood et al., 2010; Lipsett and Campleman, 1999; Steenland et al., 1996). Other clinical studies have also supported that infection-associated inflammation may be a significant risk factor for lung cancer. Other inflammatory processes inducing lung epithelial hyperplasia and malignant change have also been implicated in the pathogenesis of lung cancer. For example, one population-based cohort study has reported that cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis) was associated with an increased risk of lung cancer (Hubbard et al., 2000).

The potential "dose-response" effect between cumulative episodes of influenza and the risk of lung cancer is another important finding of this study. This may echo the potential link between lung cancer carcinogenesis and inflammation attributable to influenza infection. The dose-dependent effect identified in

Table 4
Sex differences in adjusted odds ratios for lung cancer and exposure to influenza.

Variable	Men			Women		
	Adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Influenza			0.0015			0.0172
Non-exposure	ref			ref		
Exposure	1.09	1.04–1.16		1.08	1.01–1.15	
Timing of Influenza			<0.0001			0.0036
Non-exposure	ref			ref		
Recent exposure	1.24	1.14–1.35		1.18	1.07–1.31	
Former exposure	1.01	0.94–1.08		1.02	0.94–1.11	
Counts of Influenza episodes			<0.0001			0.1208
Non-exposure	ref			ref		
1-2	1.04	0.97–1.11		1.07	1.00–1.16	
3-4	1.13	0.98–1.31		1.11	0.94–1.32	
5+	1.37	1.20–1.56		1.09	0.92–1.30	

Table 5
Age differences in adjusted odds ratios for lung cancer and exposure to influenza.

Variable	40–64 years old			65 years and older		
	Adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Influenza			0.0009			0.0253
Non-exposure	ref			ref		
Exposure	1.11	1.05–1.19		1.07	1.01-1.13	
Timing of Influenza			<.0001			0.0090
Non-exposure	ref			ref		
Recent exposure	1.32	1.20–1.46		1.14	1.05–1.24	
Former exposure	1.00	0.92–1.09		1.02	0.95–1.09	
Counts of Influenza episodes			0.0004			0.0410
Non-exposure	ref			ref		
1-2	1.07	1.00–1.15		1.04	0.97–1.11	
3-4	1.18	0.99–1.40		1.08	0.93–1.25	
5+	1.35	1.14–1.60		1.19	1.04–1.36	

the current study suggests that viral oncogenesis may occur through a "hit-and-run" mechanism that transforms cellular phenotypes (McDougall, 2001), or through the traditional theories of two "hits" and multiple "hits" of carcinogenesis (Ashley, 1969). Further in vitro and in vivo investigations are needed to investigate these concepts and to broaden the understanding of lung cancer carcinogenesis, and to explore potential novel solutions to prevent and treat lung cancer.

This study has several strengths, including the large size, the use of a cancer registry to ascertain lung cancer cases, and the sophisticated measurements of influenza episodes. However, several limitations need to be addressed as with other observational studies based on a claims database. First, the diagnosis of influenza virus infection was determined by clinicians and rapid influenza diagnostic tests (RIDTs). Although RIDTs have been reported to have a positive predictive value (PPV) of 99.5% and negative predictive value of 85.3% in screening for influenza virus, the risk of false-positive results using such assays is still under debate (Olsen et al., 2014). Therefore, overestimation of the number of influenza virus infection episodes may have occurred. Second, although we adjusted for numerous concomitant comorbidities, data on some environmental risk factors were unavailable in the NHIRD (e.g., smoking status). Smoking has been proven to be an important risk factor for lung cancer, so lack of valid information on smoking may lead to residual confounding. Therefore, we adopted the approach used by previous studies without information of smoking status (Kharazmi et al., 2012; Ung et al., 2018; Cheung et al., 2018), and used chronic obstructive pulmonary disease (COPD), a smoking-related lung disease, as a proxy to try to partially account for the effect of smoking. In our study, COPD was included in the matching variable (disease risk score) and was also one of the adjusted variables in the multivariate conditional logistic regression models to partially adjust the effect of smoking. Furthermore, we also conducted a subgroup analysis stratified by sex. Since national statistics provided by Health Promotion Administration, Ministry of Health and Welfare, Taiwan (2019) have shown that the prevalence of smoking was much lower in women than in men (e.g., women 3.3% versus men 32.5% in year 2013), the effect of smoking may be less significant in women. According to our subgroup analysis, although the risk estimate was slightly higher in men than in women, the association between influenza and lung cancer existed in both male and female patients. These findings suggested that smoking may play a role in our study, but it could not fully explain the association we found. Nevertheless, future research using other data sources which collect information on patients' smoking habits is warranted to validate our findings. Particularly, it would be of interest to test the current hypothesis in smokers and never smokers. Third, using a retrospective observational study design, we could not rule out the possibility that imaging tests or physician visits during an episode of influenza may trigger the diagnosis of lung cancer. We have excluded the influenza diagnosis within 3 months (primary analysis) or 6 months (sensitivity analyses) prior to the index date, which may reduce the influence of detection bias, and all the analyses have shown associations between influenza and lung cancer. However, further investigations are still required to determine whether the increased risk of lung cancer is related to influenza or caused by detection bias.

Conclusion

Influenza infection was associated with an increased risk of lung cancer, and the risk increased with cumulative exposure to influenza. More in vitro and in vivo investigations are warranted to

validate our findings and to better understand the mechanisms behind this potential association.

Funding

This work was supported by the research grants from Ministry of Science and Technology, Taiwan (MOST 104-2410-H-002-225-MY3). The funders had no role in study design, data collection and analysis, preparation of the manuscript, and decision to publish.

Author contributions

Weng CF, Ling TY, Chen LJ, Lin CW, Chen HM, Lee HHC and Hsiao FY, contributed to the study concept and design. Hsiao FY and Chen HM acquired and analyzed the data. Weng CF, Ling TY, Chen LJ, Lin CW, Lee HHC and Hsiao FY interpreted the data. Weng CF, Chen LJ, Lin CW, Chen HM, and Hsiao FY drafted the manuscript. Lee HHC, Ling TY and Hsiao FY revised the manuscript. All authors read and approved the final manuscript.

Disclosure of conflicts of interests

All authors have no conflicts of interest that are directly relevant to the content of this study.

Acknowledgements

We thank the National Health Insurance Administration (NHIA) and Health and Welfare Data Science Center (HWDC) for making the databases used in this study available. The content of this article does not represent any official position of the NHIA or HWDC. The authors have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.07.030.

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