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Patients with spontaneous pneumothorax have a higher risk of developing lung cancer

A STROBE-compliant article

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Abstract

Lung cancer is a common malignancy worldwide, and risk factors include bronchitis, asthma, tuberculosis, smoking, and air pollution. These are also risk factors for spontaneous pneumothorax, a benign disease. We hypothesized that patients who experience a spontaneous pneumothorax have a greater risk to develop lung cancer, and designed a study to determine if this is so.

We used the population-based Taiwan Health Insurance Research Database to perform a retrospective cohort study. The database includes more than 99% of the population of Taiwan. We established a 27,405-person pneumothorax cohort and a 109,620 person comparison cohort with data from 2000 to 2009 to evaluate the relationship between spontaneous pneumothorax and lung cancer.

Multivariable analysis showed that patients who have had a spontaneous pneumothorax have a greater relative risk to develop lung cancer. The overall hazard ratio was 2.09 (95% confidence interval 1.69-2.58) adjusted by age, gender, hypertension, diabetes mellitus, and chronic lung diseases such as chronic obstructive pulmonary disease, tuberculosis, asthma, bronchitis, and emphysema. A dose effect was present; a high frequency of spontaneous pneumothorax was associated with a greater relative risk to develop lung cancer. If the spontaneous pneumothorax frequency was greater than 2 times per year, the hazard ratio was 34.09 (95% confidence interval 22.74-51.10)

Patients with spontaneous pneumothorax have an increased relative risk to develop lung cancer, especially among patients 35 to 49 years of age. The more frequent the occurrence of spontaneous pneumothorax, the greater the relative risk of lung cancer. If the spontaneous pneumothorax frequency was greater than 2 times per year, the increase in risk of lung cancer was more than 30-fold.

Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IGF-1 = insulin like growth factor 1, TB = tuberculosis.

Keywords: spontaneous pneumothorax, lung cancer, risk factor

1. Introduction

Lung cancer is a common malignancy worldwide, and a leading cause of cancer-related deaths, especially in developed countries. The incidence is reported to be 47 per 100 thousand people, with a 5-year-survival rate of approximately 15%.[1,2] Studies have revealed the relationship between lung cancer and chronic lung diseases such as bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), tuberculosis (TB), and asthma.[2–5] Patients with those diseases have an increased risk to develop lung cancer. Spontaneous pneumothorax, a benign disease, is also associated with the aforementioned chronic lung disease, especially among elder people.[6] Many studies have found that pulmonary neoplasms can result in spontaneous pneumothorax.[7–12] Additionally, spontaneous pneumothorax can be the first sign of lung cancer.[13] However, there have been lacks of studies examining the relative risk of developing lung cancer in patients who experience spontaneous pneumothorax. We hypothesized that patients who experience a spontaneous pneumothorax have a greater risk to develop lung cancer, and designed a study to determine if this association exists.

2. Material and Methods

The stydy had been approved by Medical Ethics Commette of China Medical University Hospital, Taichung, Taiwan.

2.1. Data source

The Taiwan National Health Insurance program is a single-payer and universal insurance program implemented in 1996, and covers almost 99% of the population of Taiwan since 1998. The

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Health Insurance Research Database includes annual registration files and original claim data for reimbursement and managed by the National Health Research Institutes. All personal identification information is encrypted to protect patient privacy before data is released for research. The National Health Research Institutes creates a scrambled, anonymous identification number to connect each individual's information, including gender, birth date, and registry of medical services.

In this research, disease history was collected from in-patient files and catastrophic illness registry. Disease was defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

2.2. Study population

This research was designed a population-based retrospective cohort study. We created a pneumothorax cohort which included newly diagnosed spontaneous pneumothorax and spontaneous tension pneumothorax (ICD-9-CM 512.0 and 512.8) from the years 2000-2009. Every patient had a index date set on half year after the date pneumothorax was diagnosed. If the included patients had got any cancer before the index date, they would be excluded from pneumothorax cohort. The comparison cohort was randomly matched by gender, age and the year of the index date in a 4-fold frequency from the individuals without spontaneous pneumothorax in the Health Insurance Research Database. The research excluded individuals with cancer occurrence before the index date. The event of interest was subsequent lung cancer (ICD-9-CM 162), and data was obtained from the catastrophic illness registry. Follow-up was terminated at the development of lung cancer, withdrawal from insurance, or December 31, 2010. In total, there were 27,405 persons in the pneumothorax cohort and 109,620 in the comparison cohort.

The confounding factors were patient demographic characteristic and lung cancer-associated comorbidities. The associated comorbidities included hypertension (ICD-9-CM 401-405), diabetes mellitus (DM, ICD-9-CM 250), TB (ICD-9-CM 010-018), COPD (ICD-9-CM 496), asthma (ICD-9-CM 493), chronic bronchitis (ICD-9-CM 490-491), and emphysema (ICD-9-CM 492). These were identified from in-patient files for evaluation.

2.3. Statistical analysis

The mean and standard deviation for continuous variable and number and percentage for category variables were presented to describe the distribution of the pneumothorax and comparison cohorts. The t-test for continuous variables, and chi-square test for category variables, were used to test differences of the 2 cohorts. The total lung cancer incidence and demographic-specific, comorbidity-specific incidence of lung cancer for 2 study cohorts by per 10,000 person-years was calculated. The product-limit method was used to estimate the cumulative lung incidence curves for the study cohorts, and the log-rank test was used to assess the difference of these 2 curves. Relative to the comparison cohort, the estimated hazard ratio (HR) and confidence interval (CI) for the pneumothorax cohort were measure by Cox's proportional hazards regression model with adjustment for potential confounding factors. The average pneumothorax occurrence was defined as the total pneumothorax occurrence frequency during the follow-up time divided by the follow-up duration (years). The pneumothorax cohort was subclassified into 3 sub-cohorts: low occurrence ($\leq$ 1 time per year), moderate occurrence (1-2 times per year) and high occurrence (>2 times per year). To measure the relationship between increasing pneumothorax occurrence and risk of developing lung cancer, we estimated the HR for every level of average pneumothorax occurrence, and considered pneumothorax occurrence as a continuous variable to test the trend by Cox's proportional hazards regression.

The analyses were performed with SAS 9.3 software (SAS Institute, Cary, NC). The cumulative incidence curve was drawn with *R* software (*R* Foundation for Statistical Computing, Vienna, Austria). The significant level set at less than .05 for 2-sided testing of the *P*-value.

3. Results

The average age (38 years) and gender ratio (84% male) of the 2 cohorts were matched well (Table 1). The proportions of comorbidities in the pneumothorax cohort were higher than in the comparison cohort.

In the pneumothorax cohort, the lung cancer incidence was 12.79 per 10,000 person-years (Table 2), and this was 1.65-fold greater than in the comparison cohort (7.71 per 10,000 person-years). The cumulative incidence curves of developing lung cancer of the 2 cohorts are shown in Figure 1. The incidence curve for the pneumothorax cohort was significantly greater than that of the comparison cohort (log-rank test, $P < .0001$). We performed adjustment for some confounding factors, such as gender, age, hypertension, DM, chronic bronchitis, TB, asthma, COPD, and emphysema. The pneumothorax cohort had a 2.09-fold increased risk of developing lung cancer compared with the comparison cohort (HR = 2.09, 95% CI 1.69-2.58). Except for the lowest age group, pneumothorax was significantly associated with increased lung cancer risk in each age group. In stratified analysis by gender, the increased risk for developing lung cancer could be found in male patients with spontaneous pneumorhorax. (HR = 2.20, 95% CI 1.76-2.74) The comorbidity-specific

Table 1

Baseline demographic data and comorbidities of the 2 groups.

Variable	Comparison cohort n = 109620	Pneumothorax cohort n = 27405	*P*-value
Age, yr*	38.1 (23.1)	38.1 (23.2)	.8482
<35	66792 (60.9)	16698 (60.9)	1.0000
35-49	11516 (10.5)	2879 (10.5)	
50-64	8540 (7.8)	2135 (7.8)	
≥65	22772 (20.8)	5693 (20.8)	
Gender			
Female	16892 (15.4)	4223 (15.4)	1.0000
Male	92728 (84.6)	23182 (84.6)	
Comorbidity			
Without any comorbidity	94001 (85.8)	18540 (67.7)	<.0001
Hypertension	6877 (6.3)	3328 (12.1)	<.0001
Diabetes	9588 (8.7)	2333 (8.5)	<.0001
Tuberculosis	594 (0.5)	1871 (6.8)	<.0001
COPD	1554 (1.4)	3482 (12.7)	<.0001
Asthma	1412 (1.3)	1710 (6.2)	<.0001
Emphysema	134 (0.1)	1941 (7.1)	<.0001
Chronic bronchitis	1444 (1.3)	2463 (9.0)	<.0001

Data are presented as mean ± standard deviation or number (percentage).
COPD = chronic obstructive pulmonary disease.
* Compared with *t*-test.

Table 2

Incidence of subsequent lung cancer and multivariate Cox proportional hazards regression analysis.

Variable	Comparison cohort			Pneumothorax cohort			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate		
Total	454	588880	7.71	173	135247	12.79	1.65 (1.38-1.97)	2.09 (1.69-2.58)
Age group								
<35	3	364112	0.08	2	92126	0.22	2.63 (0.44-15.77)	2.89 (0.48-17.29)
35-49	12	66751	1.80	10	15626	6.40	3.60 (1.56-8.34)	4.76 (2.05-11.02)
50-64	57	48404	11.78	32	10091	31.71	2.69 (1.74-4.15)	2.31 (1.38-3.87)
≥65	382	109613	34.85	129	17404	74.12	2.09 (1.71-2.55)	1.79 (1.39-2.30)
Gender								
Female	45	93778	4.80	9	21075	4.27	0.89 (0.44-1.82)	1.39 (0.63-3.03)
Male	409	495102	8.26	164	114172	14.36	1.73 (1.44-2.07)	2.20 (1.76-2.74)
Comorbidity								
Without any comorbidity*	278	512562	5.42	39	100891	3.87	0.71 (0.51-1.00)	2.29 (1.62-3.24)
Hypertension								
No	371	560446	6.62	118	125555	9.40	1.42 (1.15-1.74)	2.20 (1.70-2.84)
Yes	83	28434	29.19	55	9692	56.75	1.92 (1.36-2.70)	1.84 (1.23-2.73)
Diabetes								
No	360	537647	6.70	150	126402	11.87	1.77 (1.46-2.14)	2.28 (1.81-2.88)
Yes	94	51233	18.35	23	8845	26.00	1.36 (0.86-2.14)	1.31 (0.76-2.26)
Tuberculosis								
No	440	586697	7.50	141	128424	10.98	1.46 (1.21-1.76)	2.19 (1.75-2.74)
Yes	14	2183	64.13	32	6824	46.9	0.75 (0.4-1.41)	1.16 (0.58-2.32)
COPD								
No	424	583339	7.27	99	124554	7.95	1.09 (0.88-1.36)	2.09 (1.63-2.68)
Yes	30	5541	54.14	74	10693	69.20	1.26 (0.82-1.93)	1.51 (0.96-2.38)
Asthma								
No	434	583145	7.44	152	129498	11.74	1.57 (1.31-1.89)	2.11 (1.69-2.65)
Yes	20	5735	34.88	21	5750	36.52	1.06 (0.57-1.95)	1.46 (0.73-2.94)
Emphysema								
No	452	588358	7.68	152	126199	12.04	1.56 (1.30-1.87)	2.10 (1.69-2.61)
Yes	2	522	38.29	21	9048	23.21	0.66 (0.15-2.81)	2.45 (0.55-10.88)
Chronic bronchitis								
No	432	583531	7.40	142	128450	11.05	1.49 (1.23-1.80)	2.19 (1.75-2.76)
Yes	22	5349	41.13	31	6797	45.61	1.04 (0.60-1.79)	1.16 (0.63-2.13)

Model adjusted for age, gender, hypertension, diabetes, COPD, asthma, tuberculosis, emphysema, and chronic bronchitis.

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PYs = person-years; rate, incidence rate, per 10,000 person-years.

lung cancer incidence and estimated HRs for the study cohorts are shown in Table 2. We stratified study cohorts by DM, hypertension, COPD, asthma, chronic bronchitis, emphysema and TB to realize the effect of combined existence of those diseases. The pneumothorax cohort had a 2.29-fold increased lung cancer risk compared with the comparison cohort if those diseases were all absent (HR = 2.29, 95% CI 1.62-3.24). In every stratified of every single disease, there were not a significant different between the spontaneous pneumothorax and comparison cohorts with respect to the development of lung cancer if those diseases were present except hypertension.

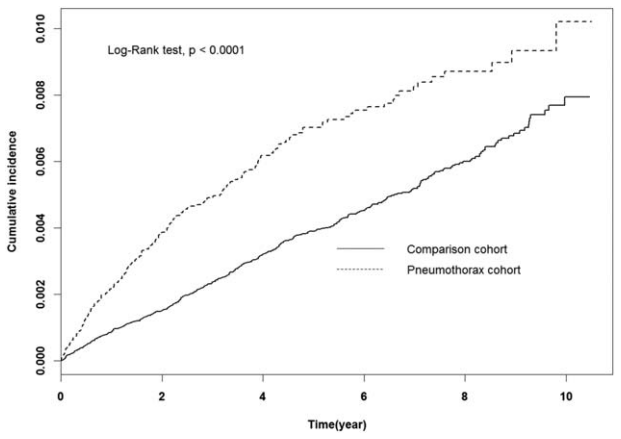

Figure 1. Cumulative incidence of subsequent lung cancer in the comparison and pneumothorax cohorts.

The relationship between frequency of pneumothorax and risk of developing lung cancer is shown in Table 3. Relative to the comparison cohort, a pneumothorax frequency of ≤ 1 time per year and 1-2 times per year were associated with increased risk of developing lung cancer (HR = 1.51 and 7.76, respectively). More importantly, a frequency of pneumothorax > 2 times per year was associated with a 34.09-fold increased risk of developing lung cancer (HR = 34.09, 95% CI 22.74-51.10). The result also indicated that the risk of developing lung cancer increased with increasing frequencies of pneumothorax occurrence (*P*-value for trend < .0001).

In this research, we also utilized sensitivity analysis to assess the risk of developing lung cancer in the study population by follow-up duration (Table 4). The results suggested that the pneumothorax cohort had a significantly increased risk of developing lung cancer compared with comparison cohort, no matter what the follow-up duration was more than 1, 2 or 3 years.

Table 3

Incidence of lung cancer and multivariate Cox proportional hazards regression analysis HR for the study cohort by average frequencies of pneumothorax.

Average frequency of pneumothorax, per year	Event	PYs	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Comparison cohort	454	588880	7.71	ref	ref
≤1	102	131951	7.73	1.00 (0.81-1.24)	1.51 (1.19-1.92)
1-2	26	2625	99.06	12.76 (8.51-19.13)	7.76 (4.97-12.11)
>2	45	671	670.72	88.20 (62.55-124.37)	34.09 (22.74-51.10)

Model adjusted for age, gender, hypertension, diabetes, chronic obstructive pulmonary disease, asthma, TB, emphysema, and chronic bronchitis.
CI = confidence interval, HR = hazard ratio, PYs = person-years; rate, incidence rate, per 10,000 person-years.
P-value for trend, <.0001.

4. Discussion

According to population-based studies from England and Taiwan, the incidence of spontaneous pneumothorax is about 13.9-24 per 100,000 persons, and the condition is more common in males (approximately 3 to 6-fold greater than in females). The age distribution is bimodal, with 1 peak at 15-25 years of age and another peak at more than 65 years of age.[14,15] The recurrence rate is up to 30% to 50%, and is related to gender, age, and smoking status.[16,17]

Pulmonary malignancy and chronic lung diseases such as bronchitis, emphysema, TB, asthma, COPD can induce spontaneous pneumothorax, especially among elder persons. In our study, there were more people with chronic lung diseases in the pneumothorax cohort. The distribution of patients with spontaneous pneumothorax was bimodal, with 1 peak at <35 years of age (60.9%), and another peak was at > 65 years of age (20.9%). These results are similar to those of prior studies.

In multivariable analysis, patients with spontaneous pneumothorax had a greater relative risk for developing lung cancer. When stratified by age, with the exception of the lowest age group, the pneumothorax cohort had a greater risk of developing lung cancer, especially among patients of 35 to 49 years old. We stratified study cohorts by several possible confounding factors to realize the effect of their combined existence. In our study, there were not a significant different between the spontaneous pneumothorax and comparison cohorts with respect to the development of lung cancer if chronic lung diseases were present. The significant difference can only been found if chronic lung diseases were not present. Although the risk for developing lung cancer increased with age, the highest relative risk was found in the group 35 to 49 years of age. This may be because the relative effect of pneumothorax for the risk of developing lung cancer is decreased in elder patients because the incidence of chronic lung diseases is greater. It can be considered that some factors are at the same time to be related with spontaneous pneumothorax, lung cancer and chronic pulmonary diseases. And those factors may be of dose effect.

Patients with disorders of blood sugar control have a greater relative risk for the development of lung cancer.[18] The growth hormone/insulin like growth factor 1 (IGF-1) axis is considered to contribute to this finding.[19] IGF-1 is secreted by stimulation of growth hormone, and combines with insulin-like growth factor binding protein-3 in the circulation.[20] IGF-1 has been shown to be an autocrine growth factor that participates in lung cancer development in in-vitro experiments of non-small cell lung cancer.[21] At the same time, insulin-like growth factor binding protein-3 can block IGF-1 signaling transduction to increase the apoptosis of cancer cells.[22] DM has been shown to be associated with a high IGF-1 level.[23] In our study, there were not a significant different between the spontaneous pneumothorax and comparison cohorts with respect to the development of lung cancer if DM was present. Just like those chronic pulmonary diseases. Is DM related with developing spontaneous pneumothorax? Are there some factors at the same time to be related with developing spontaneous pneumothorax and DM? It may be worth to further study.

Spontaneous pneumothorax is considered to be a benign disease, and can be recurrent. In order to decrease recurrent rate of pneumothorax, surgical resection of the bullae or blebs, with or without pleurodesis, is usually performed. However, the postoperative recurrent rate ranges from 8% to 16%, and more than 90% of recurrences are observed within 2 years.[18,19] Our results showed that a higher frequency of spontaneous pneumothorax was associated with a greater risk of lung cancer, and the risk was increased more than 30-fold if the frequency of spontaneous pneumothorax was more than 2 times per year. In our study population, the mean time from the first episode of spontaneous pneumothorax to lung cancer diagnosis was 2.8 ± 2.0 years. The relative risk for developing lung cancer

Table 4

Cox proportional hazards model estimated incidence of lung cancer.

	Comparison cohort			Pneumothorax cohort				
Variable	Event	PYs	Rate	Event	PYs	rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Time lag								
>1	360	587528	6.13	116	134385	8.63	1.42 (1.15-1.75)	1.87 (1.45-2.41)
>2	292	572717	5.10	74	130075	5.69	1.13 (0.87-1.46)	1.64 (1.21-2.22)
>3	214	536667	3.99	52	120860	4.30	1.09 (0.81-1.48)	1.75 (1.22-2.52)

Model adjusted for age, gender, hypertension, diabetes, chronic pulmonary disease, asthma, TB, emphysema and chronic bronchitis.
CI = confidence interval; HR = hazard ratio; PYs = person-years; rate, incidence rate, per 10,000 person-years.

should be considered when treating patients with spontaneous pneumothorax in which the frequency is more than 2 times per year.

Many chronic lung diseases are relative to spontaneous pneumothorax. Dose the occurrence of a pneumothorax alter the treatment of the underlying disease? Our data showed the occurrence of a pneumothorax is relative to higher risk of lung cancer among patients older than 35 years old, especially when the frequency is more than 2 times per year. We suggest that the main treatment of the underlying disease in not necessary to change. Is lung cancer screen among those patients valuable? It is an interesting issue. Further study is necessary. Chest CT for lung cancer screen among those patients may be considered.

In addition to chronic lung diseases, behavior and living environment are related to the development of lung cancer and spontaneous pneumothorax. A prospective study published in 1978 revealed a relationship between smoking and lung cancer and a dose effect.[20] The carcinogens in cigarette smoke can induce DNA damage and transform normal cells into cancer cells by chromosome loss at 3q21 and TP53 mutagenesis. The efficacy is also observed in second-hand smoking environments.[21,22] Smoking is also associated with pneumothorax, pulmonary disease, cardiovascular diseases, and DM.[23–25] Air pollutants such as NO_2 and O_3 are also considered risk factors for both lung cancer and spontaneous pneumothorax.[26,27]

Spontaneous pneumothorax is considered to be the result of rupture of blebs on the visceral pleura, but the pathogenesis of the blebs is unclear.[28] The possible etiologies include degradation of the elastic fibers of lung parenchyma, flux of neutrophils and macrophages as a result of smoking, and unbalance of the protease-antiprotease and oxidant-antioxidant systems.[29] The use of DNA microarrays to study gene expression in spontaneous pneumothorax revealed a relationship to inflammation, hypoxemia, and apoptosis.[30] In chronic pulmonary diseases such as COPD, the COX-2 level is up-regulated.[31,32] It shows chronic pulmonary diseases are related with inflammation also. At the same time, many studies have revealed that inflammation might be an promoter in lung cancer development.[33] Inflammation seems to be a cofactor in these diseases. In our study, lung cancer risk increased with increasing frequency of spontaneous pneumothorax. It can be considered that the pathogenesis might be chronic inflammation resulting from smoking or some air pollutions of the living environment. A limitation of this study is that data regarding behaviors and living environment were not available in the database. Further study might be necessary to realize the effect of living environment.

5. Conclusion

The results of this study revealed a higher lung cancer risk among patients with spontaneous pneumothorax, especially in the group 35 to 49 years of age. There was a dose effect between frequency of spontaneous pneumothorax and the relative risk of lung cancer. If the frequency of spontaneous pneumothorax was more than 2 times per year, the relative risk of lung cancer was increased more than 30-fold. The average time from the first episode of spontaneous pneumothorax to lung cancer diagnosis was just 2.8 ± 2.0 years. When treating patients who have a frequency of spontaneous pneumothorax of more than 2 times per year, the lung cancer risk should be considered.

Author contributions

Chien-Kuang Chen writes the manuscript. Yen-Jung Chang works for data analysis. Hsin-Yuan Fang is corresponding author, joint in interpretaton of data.

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