



Early View

Research letter

The association of lung cancer with pulmonary fibrosis

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The Association of Lung Cancer with Pulmonary Fibrosis

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Author Contributions:

N.J. and M.S. conceived the idea and designed the study. Data acquisition: N.J, D.C., and M.S. Analysis of the data: N.J. The manuscript was drafted by N.J, D.C., and M.S. All authors contributed to the data interpretation and edited the manuscript.

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Take home message: In this study using a large database of U.S. decedents, the overall presence of lung cancer was lower in those with idiopathic pulmonary fibrosis compared to those without idiopathic pulmonary fibrosis.

Introduction:

Idiopathic pulmonary fibrosis (IPF) shares several pathogenetic similarities to other fibrotic lung diseases. Patients with IPF are considered to have a higher risk of concomitant lung cancer (LC) as a result of similar risk factors which include older age, smoking, and male sex. Patients with IPF have a poor prognosis with a median survival time ranging from 2-5 years [1]. It is not yet known if LC is a significant contributor to deaths in those with IPF. To address this question, we evaluated the association between LC and IPF compared to all non-IPF decedents in the U.S. from 2004-2018.

Materials and Methods

In this large retrospective study, we used the Centers for Disease Control and Prevention Multiple Cause of Death Database. This database collects from death certificates of all U.S. residents information related to their underlying cause of death (UCD) and other conditions contributing to their death [2]. Decedents with LC and IPF were identified using ICD-10 codes similar to previous studies [3, 4]. Those less than 45 years old were excluded as the diagnosis of IPF and LC were rare in this age group. In comparing those with and without IPF, logistic regression was utilized to obtain the adjusted odds ratio (OR) as in prior studies [5]. To analyze the temporal trends, Poisson regression modeling was used (negative binomial regression was used for overdispersed data). A p-value of <0.05 was considered statistically significant. SPSS version 25 (IBM Corp, Armonk, NY) software was used for the analyses.

Results:

Overall there were 35,615,442 deaths in the U.S. from 2004-2018. LC was present in 3.38% of decedents with IPF and 6.90% of decedents without IPF. The presence of LC was significantly lower in decedents with IPF (OR 0.47, 95% CI 0.46-0.48) from 2004-2018. The odds of LC were lower in decedents with IPF in all age groups, races, both sexes (Table 1), and in the year-by-year analysis (not shown). The odds of LC remained lower in IPF decedents even after adjusting for sex and age (OR 0.50, 95% CI 0.49-0.50) or for sex and race (OR 0.47, 95% CI 0.46-0.47) using logistic regression.

We also did a reverse analysis to examine the proportion of LC decedents with IPF (0.48%) compared to non-LC decedents with IPF (1.01%). This also showed that the odds of having IPF in decedents with LC is lower (OR 0.47, 95% CI 0.46–0.48).

The mortality rate (crude) per 100,000 population from LC was 132 (156 in males and 111 in females). The mortality rate from LC decreased significantly in those without IPF and was unchanged in those with IPF from 2004-2018. As a result, the overall odds of LC with IPF showed a continued rise from 2010 to 2018 (0.43 in 2010 and 0.58 in 2018). In decedents without IPF, a negative trend was noted in LC mortality rates in both sex, all age groups, and races. In decedents with IPF, a decline in mortality rate was noted in age groups 65 to 74, and an increase in mortality rate was noted in those 75 years and older and Hispanics.

LC was listed as the UCD in 94.2% of LC decedents without IPF. In decedents with both LC and IPF, the UCD was listed as LC in 75.9% and IPF in 20.8%. In the inpatient setting, the percentage of deaths was higher in the LC decedents with IPF compared to those without but was lower in the home, hospice, and nursing home settings. For both groups, the deaths in hospice increased significantly during the study period.

Table 1. Prevalence of Lung Cancer in decedents with and without Idiopathic Pulmonary Fibrosis (IPF)

Variable	Decedents without IPF*					Decedents with IPF†					OR‡ (95% CI)	
	Total deaths	Lung Cancer Present	% Total deaths with Lung Cancer	Lung Cancer Mortality rate % change 2004-2018	p-value for trend	Total deaths	Lung Cancer Present	% Total deaths with Lung Cancer	Lung Cancer Mortality rate % change 2004-2018	p-value for trend		
Sex												
Female	18002346	1087001	6.04	-23.4	<0.001	160389	3985	2.48	-	0.30	0.40 (0.38-0.41)	
Male	17263723	1346703	7.80	-41.0	<0.001	188984	7816	4.13	-	0.32	0.51 (0.50-0.52)	
Age (years)												
45-54	2677125	164280	6.14	-48.4	<0.001	10476	294	2.81	-	0.26	0.44 (0.39-0.50)	
55-64	4797685	482281	10.05	-34.8	<0.001	32043	1533	4.78	-	0.12	0.45 (0.43-0.47)	
65-74	6566472	767181	11.68	-42.0	<0.001	76494	4070	5.32	-19.1	0.04	0.42 (0.41-0.44)	
75-84	9574477	729948	7.62	-27.4	<0.001	126992	4327	3.40	+22.3	0.001	0.43 (0.41-0.44)	
≥ 85	11650310	290014	2.49	-9.2	<0.001	103368	1577	1.53	+21.8	<0.001	0.61 (0.58-0.64)	
Race												
Native-American	186275	11424	6.13	-12.4	0.02	2775	84	3.03	-	0.52	0.48 (0.38-0.59)	
Asian	738695	49661	6.72	-17.0	<0.001	8726	214	2.45	-	0.85	0.35 (0.30-0.40)	
Black	3851698	250914	6.51	-32.4	<0.001	18707	642	3.43	-	0.34	0.51 (0.47-0.55)	
White	28498575	2039321	7.16	-23.1	<0.001	291706	10302	3.53	-	0.09	0.47 (0.47-0.48)	
Hispanic	1902714	77398	4.07	-31.2	<0.001	26903	538	2.00	+35.0	0.03	0.48 (0.44-0.52)	
Underlying Cause of Death												
IPF	n/a	n/a	n/a	n/a	n/a	n/a	1863	n/a	-	0.92	n/a	
Lung cancer	n/a	2292943	n/a	- 28.7	<0.001	n/a	8956	n/a	-	0.40	0.19 (0.18-0.20)	
Pneumonia	n/a	1023	n/a	-	0.14	n/a	19	n/a	-	1.00	3.83 (2.43-6.04)	
Place of Death												
Inpatient	n/a	700652	n/a	-45.8	<0.001	n/a	5625	n/a	-	0.44	2.25 (2.17-2.33)	
Home	n/a	993905	n/a	-22.5	<0.001	n/a	3687	n/a	-	0.11	0.66 (0.63-0.68)	
Hospice	n/a	211291	n/a	+1130.2	<0.001	n/a	847	n/a	+8880.0	<0.001	0.81 (0.76-0.87)	
Nursing Home	n/a	331624	n/a	-43.0	<0.001	n/a	896	n/a	-	0.55	0.52 (0.49-0.56)	

*: n=35,266,069; †: n=349,373; ‡: the overall odds of lung cancer with IPF compared to without IPF.

OR = Odds Ratio, CI = Confidence Interval.

International Classification of Diseases-10 codes used for UCD are as follows: pulmonary fibrosis (J84.1, J84.9), lung cancer (C34-C34.9), pneumonia (J09-J18.9)

Similar to prior studies, ICD-10 codes were used to identify and exclude patients with underlying connective tissue diseases (M32-M35, M35.1, M35.5, M35.8-M36, M05-M08.9), radiation fibrosis (J70.1), sarcoidosis (D86-D86.9), pneumoconiosis (J60-J65), and hypersensitivity pneumonitis (J67-J67.9).

If no data are shown for % change in rate, the regression analysis of the data did not indicate a significant departure from a linear trend during the analysis period.

Discussion:

Our study is the largest to date comparing the association between IPF and LC. In our study, the prevalence of LC was 53% lower in decedents with a listed diagnosis of IPF compared to those without. This finding was observed irrespective of sex, age group, race, or year of death. Our findings are consistent with a previous study by Wells et al. that reported LC in 4.8% of decedents with IPF compared to 6.5% decedents in the general U.S. population from 1979-1991 [6].

Possible explanations for the lower odds of LC with IPF are a lower prevalence of LC in patients with IPF or improved survival in those with LC and IPF. Previous studies have shown that patients with both IPF and LC have a shorter survival time [7, 8]. This is likely due to surgical procedures and treatments for LC, which have both been associated with acute exacerbations of IPF [7]. As noted in this study, the mortality rates for LC patients without IPF improved over the study period, but in those with IPF and LC, a similar improvement was not noted. Therefore, the likely explanation for our findings is the lower prevalence of LC in patients with IPF. In contrast to our findings, two previous studies in European cohorts reported an increased incident rate of LC in patients with IPF compared to the general population [9, 10]. A systematic review evaluating comorbidities in IPF reported a wide range of LC prevalence rates ranging from 3-48% [11]. The majority of these studies were single-centered with small sample sizes, and therefore selection and referral bias could have influenced the results. Our study population was significantly larger than those in previous studies. In IPF compared to the general population, the higher LC incident rate but lower prevalence could also be explained by the shorter survival time associated with IPF. Ascertainment and surveillance biases may have contributed to the higher reported incidence since IPF patients are more likely to seek evaluation sooner due to respiratory symptoms and thus have chest CT scans performed more frequently. Our non-IPF decedent group also likely represents a sicker population (similar to the IPF patients) and is, therefore, a more appropriate comparison in contrast to the prior studies where the control group was a live population. Presumably, the frequency of lung cancer among decedents exceeds that in a live population.

In a recent study using the UK IPF registry, LC was present in only 0.6% of patients with IPF [12]. Similar to our estimates, in recent studies of IPF patients admitted to the ICU, LC was reported in 2.3-3.5% of patients [13, 14]. Since both LC and IPF have a short survival time, the lower prevalence reported in these studies and ours is likely because those with LC or IPF die before the other condition can develop. Unfortunately, we did not have data on the duration of the disease to determine whether long-term IPF survivors have different rates of LC prevalence than short-term survivors. However, given that our study extended over a fifteen-year time period, we believe that our reported rates are reliable.

Consistent with other studies, we noted declining lung cancer-related mortality rates in the non-IPF decedents [15]. However, in the IPF decedents, the overall rates were unchanged. The decreasing mortality rates in the 65 to 74 years age group is likely due to improved survival of patients with both IPF and lung cancer in this age group. The increasing mortality rates in those 75 years and older are likely due to improved diagnosis or increased documentation of both diseases. The increase in LC rates in Hispanics with IPF is likely due to improved access to medical care facilitated by the Affordable Care Act.

We noted that the odds of having LC listed as the UCD was even lower in IPF decedents compared to those without IPF. This is likely because a significant percentage of IPF patients experience an acute exacerbation and/or pneumonia prior to the death and are therefore likely to have those diagnoses listed as the UCD instead of LC. In the IPF and LC group, 20.8% of decedents had IPF listed as the UCD. Although only a small percentage of decedents had pneumonia listed as the UCD in both groups (0.24% of LC decedents without IPF and 1.16% of LC decedents with IPF), the OR was higher in the IPF group (3.83, 95% CI 2.43-6.04).

The strength of this study is the evaluation of the whole U.S. population and the large numbers. The main drawback is that we are not able to verify the accuracy of the diagnosis or the documentation on the death certificate. Since the diagnosis of IPF may require multidisciplinary discussion and/or surgical lung biopsy, it is possible that under-reporting and misdiagnosis may have occurred. LC in early stages or remission could also be under-reported, however, this would likely not be affected by whether a person has IPF or not. Our findings are unlikely due to random chance alone given the large numbers. To support this claim, we analyzed the

prevalence of LC in decedents with chronic obstructive pulmonary disease, a pulmonary condition that is associated with a higher prevalence of lung cancer. The overall odds of having LC were higher in those with COPD (OR 1.59, 95% CI 1.58–1.60) compared to those without COPD. In summary, we noted that the prevalence of LC is lower in decedents with IPF compared to those without IPF.

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