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Prevalence of lung cancer in patients with interstitial lung disease is higher than in those with chronic obstructive pulmonary disease

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Abstract

We aimed to explore lung cancer prevalence in interstitial lung disease (ILD) patients with or without connective tissue disorder (CTD) and idiopathic pulmonary fibrosis (IPF) in comparison with chronic obstructive pulmonary disorder (COPD).

We evaluated lung cancer prevalence associated with ILD and IPF using Korean Health Insurance Review and Assessment Service (HIRA) data from January to December 2011. This database (HIRA-NPS-2011–0001) was sampled using random sampling of outpatients; 1,375,842 sample cases were collected, and 670,258 (age ≥ 40 ys) were evaluated. Patients with ILDs, IPF, CTD, or COPD were identified using the International Classification of Disease-10 diagnostic codes.

Lung cancer prevalence rates per 100,000 persons for the sample population and those with ILD, IPF, CTD-ILD, and COPD were 420, 7334, 7404, 7272, and 4721, respectively. Lung cancer prevalence was significantly higher in those with ILD than in those with COPD ($P < .01$).

More attention should be paid to lung cancer development in those with ILD as well as COPD.

Abbreviations: COPD = chronic obstructive pulmonary disease, CTD = connective tissue disorder, HIRA = Health Insurance Review and Assessment, ICD = International Classification of Disease, ILD = interstitial lung disease, IPF = idiopathic pulmonary fibrosis, NHI = National Health Insurance.

Keywords: interstitial lung disease, lung cancer, prevalence

1. Introduction

Liebow classified idiopathic interstitial pneumonias (IIPs) into clinically and histologically distinct groups.[1] The International Classification of Disease (ICD)-9 provides no specific code for interstitial lung fibrosis other than idiopathic interstitial fibrosis, and the ICD-10 specifies interstitial lung diseases (ILD) with fibrosis as J84.1. Until the 1990 s, idiopathic pulmonary fibrosis (IPF) included a heterogeneous group of different ILDs. Recently, a more accurate ILD definition was provided by the 2011 ATS/ERS/JRS/ALAT statement of IPF diagnosis,[2] but diagnosis of IIPs except for IPF still required lung biopsy.[2–4]

Both code J84.1 (interstitial pulmonary diseases with fibrosis) and J84.9 (interstitial pulmonary disease, unspecified) were regarded as appropriate codes for IPF.[5] In contrast, based on Medicare claim data, 20% of cases of ICD-9 code 516.3 (idiopathic fibrosing alveolitis) were regarded as IPF.[6] Most of the coding for J84 is based on chest radiography or chest computerized tomography (CT) scan findings. When the 2011 ATS/ERS/JRS/ALAT statement applied for ICD-10 code J84, only 3.5% of the patients were classified as having IPF from all ILDs.[7] Unclassified ILDs have much higher prevalence than well-defined IPF. However, there was no clear clinical insight into this disease category of ILD with or without fibrosis.

Protein kinases known to play important roles in many aspects in malignant tumors such as vascular endothelial growth factor, platelet derived growth factor, and fibroblast growth factor receptors have recently been implicated in the continued proliferation of lung fibroblasts.[8] Current evidence suggests that IPF fibroblasts can exhibit an invasive phenotype,[9] thus invading the extracellular matrix, including the alveolar basement membrane as a similar way to metastatic tumor cells. Furthermore, repetitive inflammation can lead to multiple genetic alterations affecting cellular growth, differentiation, and survival. This can include the mutation of tumor suppressor genes (p53), the activation of oncogenes, and the transformation of apoptotic genes.[10,11] Fibrosis may maintain continuous stimulation of lung cells regardless of its morphology defined by CT scan. We therefore hypothesized that ILD, which reflects pulmonary fibrosis, may be associated with lung cancer.

Limited epidemiologic data are available on the occurrence of lung cancer in patients with ILD and IPF after the introduction of the 2011 ATS/ERS/JRS/ALAT statements. These statements may help to separate ILD from IPF. We aimed to explore lung cancer prevalence

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in ILD patients with or without CTD and IPF in comparison with chronic obstructive pulmonary disorder (COPD).

2. Methods

2.1. Subjects and study design

This is a cross sectional, population-based study data collected from the Korean Health Insurance Review and Assessment Service (HIRA) national database. We evaluated the prevalence of lung cancer associated with ILD and IPF utilizing HIRA data from January to December 2011. The database (HIRA-NPS-2011–0001) was based on stratified random sampling of outpatients from the whole population. There were 1,375,842 sample cases, and 670,258 of these (age ≥40 years) were evaluated. Patients with ILDs, IPF, CTD, or COPD were identified based on the ICD-10 diagnostic codes. This study was approved by the institutional review board at Dongsan Hospital, Keimyung University School of Medicine. Consent was not obtained since patient information was anonymized.

2.2. Case identification

Cases were included in the study based upon diagnostic and treatment evidence of ILDs and IPF. All cases were included when both diagnostic and procedure codes were identified simultaneously. These processes were performed automatically using a computer-based program. The ICD-10 is used as a reference in the medical diagnosis of diseases and within the health insurance system. We used the J84 ICD-10 code for other interstitial pulmonary diseases, excluding drug-induced ILDs, interstitial emphysema, connective tissue disorder (CTD), and lung diseases caused by external agents. The J84.1 ICD-10 code was used for interstitial pulmonary diseases with fibrosis, excluding chronic pulmonary fibrosis due to inhalation of chemicals, gases, fumes, or vapors and following radiation. If cases had both J84.9 and J84.1 codes, we regarded them as fitting under J84.1; if they had both J84.9 and J84.1 codes, we regarded them as fitting under J84.1. Code J84.1A (based on the 2011 international statement)[2] was specifically designed and implemented for IPF,[7] whereas C34 (ICD 10 code) was used for malignant neoplasm of bronchus and lung and J44 (ICD 10 code) for obstructive pulmonary disease. We have already classified the IPF as a specific diagnostic code (J84.1A) different from the ILD since 2009, in much the same way as the new diagnostic criteria introduced in 2011.[2] We excluded ILDs in COPD cases. Codes for identification of systemic CTD were as following; M05 for rheumatoid arthritis, M07 for psoriatic and enteropathic arthropathies, M30 for polyarteritis, M31 for other necrotizing vasculopathies, M32 for systemic lupus erythematosus, M33 for dermatopolymyositis, M34 for systemic sclerosis, M35 for other systemic involvement of connective tissue, and M45 for ankylosing spondylitis. CTD-ILD defines as any of systemic CTD with J84 codes.

2.3. Patients with COPD as control subjects

We chose COPD patients as a control group to lessen confounding bias of smoking between ILD and lung cancer because they smoke as much as ILD patients.[12]

2.4. Statistical analysis

We counted the patients diagnosed with ILD, IPF, CTD-ILD, or COPD in 2011 and calculated the prevalence rate (per 100,000). Ninety-five percent confidence intervals (CIs) were calculated using the normal approximation to the binomial distribution. The prevalence of lung cancer in ILD, IPF, and ILD-CTD patients was compared with that of COPD patients by two sample Z-test.[13] $P < .05$ were considered to be statistically significant.

3. Results

3.1. Patients with ILDs, COPD, and controls

A total of 66% of patients with ILD and 56.3% COPD controls were men. The median ages of the patients with ILD and those of the COPD controls were 68 and 69 years, respectively. Approximately 2.9% of patients with ILD and 2.1% of COPD controls had diagnoses of active tuberculosis during 2011. In addition, 2.8% of patients with ILD and 2.3% of COPD controls had previous history of thromboembolism (Table 1).

Table 1

Demographic and clinical characteristics of patients with interstitial lung disease, COPD, and sample population.

Characteristic	Sample population (n = 670,258), n (%)	ILD (n = 859), n (%)	COPD (n = 15,949), n (%)
Sex			
Male	313,781 (46.8)	570 (66.3)	9039 (56.7)
Female	356,477 (53.2)	289 (33.6)	6,910 (43.3)
Age			
Median (Q1, Q3)	53 (47, 64)	68 (59, 76)	69 (60, 76)
40–49	235,082 (35.7)	67 (7.8)	1203 (7.6)
50–59	204,200 (30.2)	161 (28.1)	2559 (27.1)
60–69	122,099 (18.4)	242 (28.1)	4332 (27.1)
70–79	79,728 (11.5)	276 (32.1)	5324 (33.3)
≥80	29,149 (4.1)	113 (13.2)	2531 (15.8)
Respiratory disease*			
Influenza and viral pneumonia (J09-J12)	3973 (0.6)	18 (2.1)	221 (1.4)
Bacterial Pneumonia (J13-J15)	7485 (1.1)	107 (12.4)	1183 (7.5)
Active tuberculosis (A15)	1486 (0.2)	25 (2.9)	335 (2.1)
Other baseline comobidities			
Malignancy (C00-C97) except lung cancer (C34)	33,740 (5.1)	144 (16.7)	2,245 (14.1)
Diabetes (E10-E14)	115,914 (17.4)	309 (35.9)	5,385 (34.3)
Chronic renal failure (N17-N19)	8576 (1.3)	50 (5.8)	723 (4.6)
Previous thromboembolism (I80.2, I80.3, I26, I26.0, I26.9, I81, I82, I82.0, I82.8, I82.9)	3092 (0.5)	24 (2.8)	367 (2.3)
previous myocardial infarction (I21, I22, I23, 25.2)	6675 (1.0)	35 (4.1)	578 (3.77)

* Between January 2011 and December 2001. Summarized based on the diagnosis at the top of the lists of International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) codes of respiratory diseases.

COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease.

Table 2

Age and gender distribution of the study population and age- and gender-specific lung cancer prevalence in the sample population in Korea.

	Men				Women				Total			
Age, years	Population (n)	Cases (n)	Prevalence (1/100,000)	95% CI	Population	Cases	Prevalence (1/100,000)	95% CI	Population (n)	Cases (n)	Prevalence (1/100,000)	95% CI
40–49	115261	154	133.6	112.5–154.7	119821	85	70.9	55.9–86.0	235082	239	101.7	88.8–114.5
50–59	99631	343	344.3	307.9–380.6	104569	205	196.0	169.2–222.9	204200	548	268.4	245.9–290.8
60–69	57841	573	990.6	909.9–1071.4	64258	247	384.4	336.5–432.2	122099	820	671.6	625.8–717.4
70–79	32588	567	1739.9	1597.9–1881.9	47140	292	619.4	548.6–690.3	79728	859	1077.4	1005.8–1149.1
>80	8460	194	2293.1	1974.2–2612.1	20689	161	778.2	658.5–897.9	29149	355	1217.9	1092.0–1343.8
Total	313781	1831	583.5	556.9–610.2	356477	990	277.7	260.4–295.0	670258	2821	420.9	405.4–436.4

CI = confidence interval.

3.2. Lung cancer prevalence in the groups

In the random samples from the NHI database during 2011, there were 670,258 cases aged ≥40 years from a total of 1,375,842. ILD, IPF, CTD-ILD, and COPD cases made up 0.12%, 0.01%, 0.01%, 2.37% of the sample population, respectively (Table 2).

Lung cancer was detected in 2,821 (0.42%) cases among those aged ≥40 years in the sample population. Lung cancer prevalence was 420.9 per 100,000 individuals. The number of cases was highest in the 70 years age group, but the highest prevalence rate was in those aged ≥80 years (Table 2). In the sample population, the prevalence of lung cancer was higher in men than women in all age groups. The difference in the prevalence of lung cancer among men and women also increased with age.

Of 859 ILD patients, 63 cases had lung cancer (7.3%). The number of cases and prevalence were highest in the 60 years age group (Table 3). In ILD patients, the prevalence of lung cancer was higher in men than women in all age groups.

IPF was found in 108 cases in this study population, among which 8 cases (7.4%) involved lung cancer. The number of cases was highest in the 60 years age group, but the highest prevalence rate was found in the 50 years. In this study population, no lung cancer was found in cases of women with IPF.

ILD with CTD was found in 110 cases, among which 8 cases (7.2%) involved lung cancer. In this study population, 6 lung cancer patients were women, and 2 were men. Women with CTD-ILD had a higher prevalence of lung cancer than men.

COPD was found in 15,949 cases, among which 753 cases (4.7%) involved lung cancer (Table 3). In COPD patients, the prevalence of lung cancer was higher in men than women in all age groups.

3.3. Lung cancer prevalence among the groups

Lung cancer prevalence in those with ILD was significantly higher than in those with COPD ($P < .01$) (Table 4). The prevalence of lung cancer was significantly higher in women with ILD ($P < .01$) and CTD-ILD ($P < .01$) compared with COPD. However, no significant difference was found in men (Table 4).

Table 3

Prevalence of lung cancer according to age group and sex in patients with ILD, IPF, CTD-ILD, and COPD.

Age groups, years	Population Men	Cases	Prevalence (1/100,000)	95% CI	Population Women	cases	Prevalence (1/100,000)	95% CI	population Total	cases	Prevalence (1/100,000)	95% CI
ILD												
40–49	40	2	5000	0.0–11754.1	27	2	7407.4	0.0~17285.8	67	4	5970.1	296.8–11643.5
50–59	109	6	5504.5	1223.0–9786.2	52	1	1923.0	0.0–5655.8	161	7	4347.8	1197.8–7497.9
60–69	173	21	12138.7	7272.3–17005.2	69	4	5797.1	2832.0–11311.0	242	25	10330.5	6495.9–14165.2
70–79	181	16	8839.7	4704.2–12975.3	95	5	5263.1	772.9–9753.4	276	21	7608.6	4480.7–10736.7
>80	67	4	5970.1	2968.0–11643.5	46	2	4347.8	0.0–10241.0	113	6	5309.7	1175.5–9444.0
total	570	49	8596.4	6295.3–10897.7	289	14	4844.2	2369.0–7319.6	859	63	7334.1	5590.8–9077.5
IPF												
40–49	2	0	0		1	0	0		3	0	0	
50–59	13	3	23076.9	173.9–45980.0	5	0	0		18	3	16666.6	0.0–33883.2
60–69	28	4	14285.7	1324.5–27247.0	10	0	0		38	4	10526.3	768.7–20283.9
70–79	35	1	2857.1	0.0–8376.5	7	0	0		42	1	2380.9	0.0–6991.6
>80	5	0	0		2	0	0		7	0	0	
total	83	8	9638.5	3289.5–15987.6	25	0	0		108	8	7407.4	2468.2–12346.6
CTD-ILD												
40–49	3	0	0		12	0	0		15	0	0	
50–59	8	1	12500.0	0.0–35417.2	19	2	10526.3	0.0~24325.6	27	3	11111.1	0.0–22965.2
60–69	16	1	6250.0	0.0–18110.8	18	2	11111.1	0.0–25629.4	34	3	8823.5	0.0~18357.4
70–79	6	0	0		20	1	5000.0	0.0–14551.7	26	1	3846.1	0.0–11238.1
>80	4	0	0		4	1	25000.0	0.0–67434.5	8	1	12500.0	0.0–35417.2
Total	37	2	5405.4	0.0–12691.5	73	6	8219.1	1918.7–14519.7	110	8	7272.7	2419.8~12125.7
COPD												
40–49	637	19	2982.7	1661.7–4303.8	566	5	883.3	112.5–1654.3	1203	24	1995.0	1204.9–2785.2
50–59	1512	83	5489.4	4341.3–6637.5	1047	20	1910.2	1081.1~2739.4	2559	103	4025.0	3263.5–4786.5
60–69	2678	188	7020.1	6052.5–7987.8	1654	31	1874.2	1220.7–2527.8	4332	219	5055.4	4403.0~5707.8
70–79	3033	223	7352.4	6423.6–8281.3	2291	70	3055.4	2350.7–3760.2	5324	293	5503.3	4890.8–6115.9
>80	1179	77	6530.9	5120.7~7941.3	1352	37	2736.6	1867.0–3606.3	2531	114	4504.1	3696.2–5312.1
total	9039	590	6527.2	6018.1–7036.5	6910	163	2358.9	2001.1–2716.7	15949	753	4721.2	4392.1–5050.5

Table 4

Prevalence of lung cancer in 100,000 persons by sex in patients with COPD, ILD, IPF, and CTD-ILD.

	Men				Women				Total			
	Population (n)	Cases (n)	Prevalence	P*	Population (n)	Cases (n)	Prevalence	P*	Population (n)	Cases (n)	Prevalence	P*
COPD (reference)	9039	590	6527.3		6910	163	2358.9		15949	753	4721.3	
ILD	570	49	8596.5	.05	289	14	4844.3	<.01	859	63	7334.1	<.01
IPF	83	8	9638.6	.25	25	0	0.0	.43	108	8	7407.4	.19
CTD-ILD	37	2	5405.4	.78	73	6	8219.2	<.01	110	8	7272.7	.20

COPD = chronic obstructive pulmonary disease, CTD = connective tissue disorder, ILD = interstitial lung disease.

* The prevalence of lung cancer in ILD, IPF, and ILD-CTD patients was compared with that of COPD patients by 2 sample Z-test.

3.4. Man-to-woman lung cancer prevalence ratio among the groups

The man-to-woman ratio of lung cancer prevalence in the whole population was 2.1. The ratio for interstitial lung disease and ILD with connective tissue disorder was lower than for the whole population, while it was higher for COPD (Fig. 1). In the IPF group, all of the lung cancer cases were in men.

4. Discussion

This is a population-based study, which provides new data supporting the association of ILD and IPF with lung cancer. The prevalence rates of lung cancer in patients with ILD, IPF, CTD-ILD were 7334, 7407, and 7272 per 100,000 individuals, respectively, whereas those in patients with COPD and the whole population were 4721 and 420, respectively.

The prevalence rate of lung cancer in those with IPF ranged from 4.8% to 48%.[14–17] This wide range of lung cancer prevalence in IPF might be due to differing diagnostic criteria and study design. Recent studies demonstrated that IPF is a significant risk factor for lung cancer.[16–18] The present study also showed prevalence rate for lung cancer in those with IPF to be 17.5 folds higher compared with sample population. Not only IPF but also ILD showed higher prevalence rate for lung cancer to be 17.4 folds. This was unexpectedly high for lung cancer in those with ILD. We suspect that diseases affecting the lung interstitium without a specific cause would be similar diseases and have similar characteristics. We also suspect that diseases affecting the lung interstitium without a specific cause would have similar disease characteristics as suggested by genetic study.[19]

In 2012, Korean national statistics showed the lung cancer prevalence in the whole population to be 106/100,000 individuals.[20] If we confine this to those older than 40 years old, lung cancer prevalence reaches 223 per 100,000 individuals. National cancer statistics used the denominator as a whole population. However, this HIRA data was based on people who visited a clinic at least once in the 2011 calendar year. This may lead to overestimation of lung cancer prevalence in HIRA data or underestimation of lung cancer prevalence in the national cancer statistics. Although there will be discrepancy between this sample population data and national data, comparison of lung cancer prevalence among groups in the sample data would be possible.

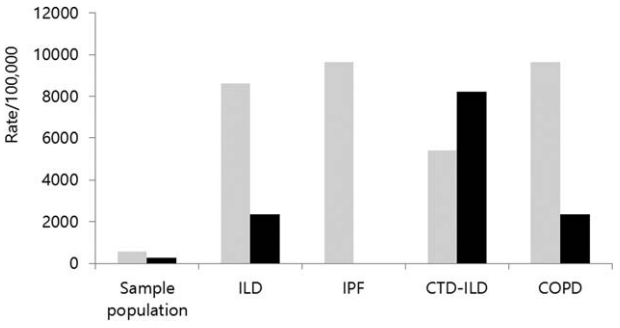

Figure 1. Male-to-female lung cancer prevalence rates between the groups. COPD = chronic obstructive pulmonary Disease, CTD = connective tissue disorder, ILD = interstitial lung disease, Gray bar denotes male and black bar denotes female.

A previous study showed that those with ILD had 7 times higher risk for developing lung cancer in comparison to general population.[16] It matched controls by smoking status, which we could not control for. This may explain why lung cancer risk was 18 times higher than in the controls. Another study demonstrated a 14-times-higher lung cancer risk in those with cryptogenic fibrosing alveolitis compared with the general population,[21] consistent with the present study. Korean national cohort data showed that 68% of those with COPD were smokers[22]; 72% of women but only 12% of men with COPD had never smoked.[23] About 64% of IPF patients in Korea were smokers.[24] COPD and IPF in Korea had frequencies of history of smoking of 68% and 64%, respectively. In Korea, the frequency of smokers in CTD-IPF patients was 28%,[1] and in CTD-ILD patients it was 24%, with 59% of smokers in ILD patients.[25] When considering similar or lower frequency of cigarette smoking, ILD has higher lung cancer prevalence than COPD in the present study.

The risk of patients with COPD developing lung cancer is well known.[12,26,27] There have been comparisons of lung cancer risk between COPD and ILD or fibrosis patients,[14,15] but the results were contradictory. However, the present population-based study showed that those with ILD had about 1.5 times-higher prevalence of lung cancer than those with COPD. This indicates that it is worth paying attention to lung cancer screening in those with ILD. We suspect that changes in the lung interstitium have higher potential to develop into lung cancer than changes in the airway.

Many studies demonstrated that lung cancer was associated with specific lung diseases such as systemic sclerosis,[28–30] dermatomyositis/polymyositis,[31–33] rheumatoid arthritis,[34–36] and systemic lupus erythematosus (SLE).[37,38] Women were at a higher risk of developing cancer than men in those with SLE.[38,39] The present study showed that CTD-ILD has similar lung cancer prevalence compared with ILD or IPF. The man-to-woman lung cancer ratio was 0.65 in those with CTD-ILD with lung cancer (Fig. 1), in line with previous studies. We suspect that the association of lung cancer with ILD is less influenced by male sex.

Our study has a couple of limitations. First, the HIRA database provided limited available patient data regarding age, sex, year, diagnostic code, and medication code. Therefore, we could not

accurately validate patients by identification or exclusion of definition through review of the source medical records. Second, we could not control confounding effects of smoking directly because the HIRA database does not provide smoking history. However, this large-scale data may provide new insights of ILDs. Another limitation is that this study needs to confirm whether the results are replicated in other ethnic groups.

5. Conclusions

This epidemiologic study suggested that efforts should be made to carefully identify the presence or new development of lung cancer in patients with ILD.

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