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Time-dependent propensity-matched general population study of the effects of statin use on cancer risk in an interstitial lung disease and pulmonary fibrosis cohort

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ABSTRACT

Objective To determine the effect of statins on risk of cancer in patients with interstitial lung disease (ILD) and pulmonary fibrosis.

Setting We retrospectively enrolled patients with ILD and pulmonary fibrosis and divided them into two cohorts by statin use (statin users (n=10 036) and statin non-users (n=10 036)).

Participants We selected patients with ILD and pulmonary fibrosis (N=53 862) from Taiwan's National Health Insurance Research Database. Time-dependent Cox models were used to compare risk of cancer of propensity-matched statin users and non-users. Cumulative cancer incidence was analysed through Cox proportional regression. We calculated adjusted HRs (aHRs) and their 95% CIs for cancer after adjusting for sex, age, comorbidities, and use of inhaled corticosteroids, oral steroids and statins.

Results Compared with statin non-users, the aHRs (95% CIs) for statin users were 0.60 (0.55 to 0.65) for cancer, 0.52 (0.35 to 0.78) for haematological malignancy, 0.52 (0.38 to 0.72) for cancer of the head and neck, 0.73 (0.59 to 0.89) for colorectal cancer, 0.34 (0.26 to 0.43) for liver cancer, 0.39 (0.23 to 0.67) for pancreatic cancer, 0.40 (0.17 to 0.96) for skin cancer, 0.67 (0.52 to 0.87) for breast cancer, 0.27 (0.14 to 0.54) for cervical cancer, 0.37 (0.30 to 0.46) for other immunological cancers, 0.73 (0.54 to 0.98) for bladder/kidney cancer and 0.88 (0.71 to 1.09) for lung cancer.

Conclusion Statin use is associated with lower risk of cancer in the ILD and pulmonary fibrosis cohort.

Strengths and limitations of this study

- This novel study investigated the risk of cancer (particularly risk of immunological cancers) among patients with interstitial lung disease (ILD) and pulmonary fibrosis in the general population.
- Not all drugs used for ILD treatment (eg, hydroxychloroquine, interferon, anti-interleukin, azathioprine and non-steroidal anti-inflammatory drugs) were analysed.
- We did not stratify statin users by lipophilic and hydrophilic statin use for sensitivity analysis.

INTRODUCTION

Cancer is associated with immune system dysregulation, infection, environment, lifestyle and ageing. Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD) that involves lung fibroblasts and shares many similar characteristics with cancer cells. Epithelial-mesenchymal transition, excessive micro-RNA, cell-to-cell communication and signal transduction pathways characterise the pathogenesis of ILD-IPF and lung cancer.[1 2] These findings suggest that ILD, pulmonary fibrosis and lung cancer share common pathogenetic features.[1 2]

Immunological cancer includes HIV-related cancers (eg, Kaposi's sarcoma and non-Hodgkin's lymphoma) and other virus-related cancers such as oral cancer (caused by human papillomavirus (HPV)), liver cancer (caused by hepatitis B virus (HBV) or hepatitis C virus (HCV)), Hodgkin's and non-Hodgkin's lymphoma (associated with Epstein-Barr virus (EBV)), and colon cancer (irritable bowel syndrome-associated virus (IBS-V)). HIV, HPV, HBV, HCV, EBV and IBS-V are associated with ILD, fibrosis and immunological cancers.[3–7] The coronavirus is also associated with ILD and pulmonary fibrosis, suggesting that this virus may play a role in the higher mortality of patients with cancer.[8–10]

Statins have multiple pleiotropic effects (eg, suppression of inflammation, reduction of oxidative stress and reduction of T cell activation) that have implications for immunomodulatory diseases. Researchers have speculated that statins play an auxiliary role

in attenuating cancer formation in patients with ILD and pulmonary fibrosis. First, matrix metalloproteinases (MMPs) are essential in IPF progression, and the overexpression of MMPs in cancer formation, ILD and pulmonary fibrosis has been reported.[11–13] This suggests that statins that inhibit MMPs can play an auxiliary role in attenuating IPF exacerbation, leading to a lower risk of cancer formation in ILD and pulmonary fibrosis.[11–14] Second, the optimal expression of ACE2 and angiotensin 1–7 suppresses cancer formation in ILD and pulmonary fibrosis through overexpression of ACE.[15–19] An increase in interleukin 6 (IL-6) also promotes tumour formation.[20 21] Statins that play an auxiliary role in enhancing the effects of ACE2 and angiotensin 1–7 and attenuating the effects of IL-6[17 19] thus play an auxiliary role in inhibiting immunological cancers such as oral cancer, colorectal cancer, liver cancer and lymphoma evolution. Third, the epidermal growth factor receptor (EGFR), which is associated with hepatoma-related virus infections involving viruses such as HBV and HCV, is involved in the association of coronavirus with ILD and pulmonary fibrosis (eg, IPF).[22 23] Nguyen *et al*[24] reported that statins may play a supportive role in attenuating the effect of EGFR overexpression in patients with cancer. Collectively, the aforementioned findings indicate that statins are associated with a lower risk of immunological cancers in patients with ILD and pulmonary fibrosis, which are closely associated with virus infections.[8 18 25–27]

To date, no study has examined the role of statins in the risk of immunological cancer during treatment of ILD and pulmonary fibrosis. Thus, we investigated the relationship between statin use and cancer incidence in general population patients with ILD and pulmonary fibrosis.

MATERIALS AND METHODS

Patient and public involvement

Taiwan's National Health Insurance (NHI) programme was launched in March 1995 and currently provides insurance coverage to 99% of Taiwan's 23 million population. Patients included in this retrospective population-based cohort study were selected from a subset of the National Health Insurance Research Database (NHIRD). We used data from the Longitudinal Health Insurance Database 2000 (LHID 2000), which comprises 1 000 000 randomly sampled beneficiaries who are enrolled in the NHI programme. The database contains extensive inpatient and outpatient data of all insured individuals, including their demographic characteristics (eg, age, sex and socioeconomic status) and diagnostic and therapeutic information such as those relating to chest X-rays (CXRs), CT, pathology, pulmonary function tests, biochemistry data, chemotherapy, radiotherapy and mechanical ventilation. The disease codes used in the LHID 2000 correspond to those of the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. Because patients (ie, insured individuals) were deidentified to protect their privacy, informed consent was not required.

Study participants

We selected patients who were diagnosed as having ILD and pulmonary fibrosis (N=53 862) between 1 January 2000 and 31 December 2013. The ICD-9-CM diagnosis codes used to identify patients with ILD and pulmonary fibrosis were as follows: 135, sarcoidosis; 237.7, neurofibromatosis; 272.7, lipidoses; 277.3, amyloidosis; 277.8, other specified metabolic disorders including eosinophilic granuloma; 446.21, Goodpasture syndrome; 446.4, Wegener granulomatosis; 495, extrinsic allergic alveolitis; 500, coal workers' pneumoconiosis; 501, asbestosis; 502, pneumoconiosis due to other silica or silicates; 503, pneumoconiosis due to other types of inorganic dust; 504, pneumonopathy due to inhalation of other types of dust; 505, unspecified pneumoconiosis; 506.4, chronic respiratory conditions due to chemicals, gases, fumes and vapours; 508.1, chronic and other pulmonary manifestations due to radiation; 508.8, respiratory conditions due to other specified external agents; 515, postinflammatory pulmonary fibrosis; 516, other alveolar and parietoalveolar pneumonopathy; 516.30, idiopathic interstitial pneumonia not otherwise specified; 516.31, IPF; 516.32, idiopathic non-specific interstitial pneumonitis; 516.33, acute interstitial pneumonia; 516.34, respiratory bronchiolitis ILD; 516.35, idiopathic lymphoid interstitial pneumonia; 516.36, cryptogenic organising pneumonia; 516.37, desquamative interstitial pneumonia; 517.2, lung involvement in systemic sclerosis; 517.8, lung involvement in other diseases classified elsewhere; 518.3, pulmonary eosinophilia; 555.0–555.2, Crohn's disease; 558.9, granulomatous enteritis; 710, diffuse diseases of connective tissue; 710.1, systemic sclerosis; 710.2, Sjogren's disease; 710.3, dermatomyositis; 710.4, polymyositis; 714.81, rheumatoid lung; 720, ankylosing spondylitis and other inflammatory spondylopathies; and 759.5, tuberous sclerosis.[28] The incidence of lung cancer can reach 57.6% in patients with post-IPF and 36.5% in patients diagnosed synchronously as having lung cancer and IPF.[1] Patients with Crohn's disease have a higher incidence of IPF due to the association between IPF and IBS; therefore, we included Crohn's disease in our analysis.[29 30]

The date of the first diagnosis of ILD and pulmonary fibrosis was defined as the index date. According to their statin use during the study period, the enrolled patients were divided into two cohorts (N=53 862), namely statin users (n=31 738) and statin non-users (n=22 124) cohorts. Because the frequency of medication use varied among the participants, their statin use status was assessed every 6-month period. Patients with a history of cancer diagnosed before the index date (ICD-9-CM codes 140–208) were excluded.

The diagnosis of ILD and pulmonary fibrosis in Taiwan is based on clinical history, CXR, high-resolution CT and pathology.[28] The coding of ILD and pulmonary fibrosis in the NHIRD was established according to these strict standards.

Outcome variables

The main outcome was diagnosis of a new cancer. To define cancer precisely, all patients enrolled in this study were linked to the registry of the Catastrophic Illness Patient Database. Our study outcomes comprised cancers of haematology (ICD-9-CM codes 200–208), head and neck (140–149), oesophagus (150), stomach (151), colon and rectum (153 and 154, respectively), liver (155), pancreas (157), lung (162), skin (173), breast (174), cervix (180), endometrium (182), ovary (183), prostate (185), kidney (188 and 189), brain (191), thyroid (193), and other conditions that were related to immunological cancers (other immunological cancers; 172, malignant melanoma; 176, Kaposi's sarcoma).[31] All patients were tracked until cancer diagnosis, withdrawal from the NHI or the end of 2013.

Patients who withdrew from the NHI system before the end of the study period were excluded from the present study. To prevent confounding factors from influencing the cancer risk results of the study groups, patients who previously had cancer and those who received anticancer therapy were excluded from the present study. Patients who had used statins for less than 3 months were regarded as new users.

Potential comorbidities and drugs

The following potential comorbidities were included in the present study: sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illnesses, chronic kidney disease, gout, coronary artery disease and stroke. Patients' use of inhaled corticosteroids (ICS) and oral steroids (OS) for asthma or chronic obstructive pulmonary disease (COPD) was also considered. All comorbidities and drugs were diagnosed using ICD-9-CM codes, which were examined in previous studies.[32]

Statistical analysis

Differences in age, sex and comorbidities between statin users and non-users were examined using the χ^2 test. Differences in mean age were examined using t-tests. The overall incidence rate of cancer (per 1000 person-years) and the incidence rates (per 1000 person-years) specific to sex, age and follow-up time were estimated. Because the dynamic frequency of statin (hydrophilic and lipophilic statins) use may introduce bias to the study results,[17] we analysed statin use as a time-dependent covariate through the quantification of participants' statin use status for every 6-month period. Cox proportional hazards models with time-dependent exposure covariates were used to compute the HR with 95% CI. To further control for potential confounding factors, we performed sensitivity analyses to match the two groups on the basis of their propensity score at a 1:1 ratio. The propensity score was calculated according to age-related, sex-related and cancer-related comorbidities using logistic regression. Moreover, time-dependent Cox models were employed to compare the risk of cancer of propensity-matched statin users (n=10 036) and non-users (n=10 036). The Kaplan-Meier method was used to obtain the cancer incidence cumulative curves of statin users and non-users, and these curves were subsequently examined by performing log-rank tests. A two-tailed p value of <0.05 indicated statistical significance. All analyses were conducted using SAS statistical software (V.9.4).

RESULTS

The characteristics of the cohort are presented in table 1. A total of 53 862 patients with ILD and pulmonary fibrosis were enrolled in the present study. We identified 31 738 statin users and 22 124 statin non-users in the non-matched cohorts. After conducting propensity score matching, 10 036 statin users and 10 036 non-users were selected for the matched cohorts. Between the two non-matched cohorts, significant differences in age and comorbidities were observed (p<0.001). Between the two matched cohorts, significant differences were only noted for sex (p=0.02) and alcohol-related illnesses (p=0.01). The mean age of those in the non-matched cohort was 55.3 years, and approximately 56% of the study participants were women. The results are presented in figure 1, which indicates that the cumulative incidence of cancer was lower among statin users relative to statin non-users.

Time-dependent covariates in the non-matched cohort

The incidence and risk for all cancers were significantly lower among statin users relative to statin non-users (17.5 vs 24.2 per 1000 person-years), with an adjusted HR (aHR) of 0.59 (95% CI 0.55 to 0.63) after controlling for covariates. Stratification according to cancer site revealed that relative to statin non-users, statin users exhibited significantly lower risk for haematological malignancy (aHR=0.59; 95% CI 0.43 to 0.81), head and neck cancer (aHR=0.55; 95% CI 0.43 to 0.71), colorectal cancer (aHR=0.78; 95% CI 0.67 to 0.92), liver cancer (aHR=0.30; 95% CI 0.25 to 0.36), pancreatic cancer (aHR=0.42; 95% CI 0.28 to 0.63), lung cancer (aHR=0.80; 95% CI 0.67 to 0.92), breast cancer (aHR=0.62; 95% CI 0.50 to 0.78), other immunological cancers (aHR=0.35; 95% CI 0.29 to 0.41), cervical cancer (aHR=0.33; 95% CI 0.21 to 0.53), kidney cancer (aHR=0.74; 95% CI 0.59 to 0.96) and other cancers (aHR=0.61; 95% CI 0.46 to 0.80) (table 2).

Data on specific cancers that were associated with statistically significant results (table 2) were further stratified by sex, age and follow-up time. Among male patients, statin users exhibited a significantly lower risk (compared with statin non-users) for all cancers (aHR=0.61; 95% CI 0.56 to 0.67), head and neck cancer (aHR=0.57; 95% CI 0.44 to 0.75), colorectal cancer (aHR=0.70; 95% CI 0.56 to 0.87), liver cancer (aHR=0.36; 95% CI 0.28 to 0.45), pancreatic cancer (aHR=0.31; 95% CI 0.17 to 0.58) and other immunological cancers (aHR=0.40; 95% CI 0.33 to 0.50). Among female patients, statin users exhibited a significantly lower risk (compared with statin non-users) for all cancers (aHR=0.56; 95% CI 0.51 to 0.62),

Table 1 Distribution of demographic and clinical comorbid status in the study cohorts

	Non-matched							Propensity score-matched				
	Interstitial lung disease and pulmonary fibrosis							Interstitial lung disease and pulmonary fibrosis				
	Statin							Statin				
	All (N=53 862)		No (n=31 738)		Yes (n=22 124)			No (n=10 036)		Yes (n=10 036)		
Variables	n	%	n	%	n	%	P value	n	%	n	%	P value
Age, years							<0.001					0.81
<50	19 858	36.9	15 715	49.5	4143	18.7		2645	26.4	2639	26.3	
50–64	17 384	32.3	8175	25.8	9209	41.6		3813	38.0	3855	38.4	
65+	16 620	30.9	7848	24.7	8772	39.7		3578	35.7	3542	35.3	
Mean±SD*	55.3	16.7	51.3	17.9	61.2	12.7	<0.001					
Gender							0.08					0.02
Female	30 012	55.7	17 784	56.0	12 228	55.3		5244	52.3	5405	53.9	
Male	23 850	44.3	13 954	44.0	9896	44.7		4792	47.8	4631	46.1	
Comorbidity												
Sleep disorder	22 921	42.6	12 384	39.0	10 537	47.6	<0.001	4643	46.3	4603	45.9	0.57
Diabetes	10 287	19.1	2767	8.72	7520	34.0	<0.001	1959	19.5	2038	20.3	0.16
Hypertension	29 761	55.3	12 137	38.2	17 624	80.0	<0.001	6661	66.4	6585	65.6	0.26
Hyperlipidaemia	28 826	53.5	8569	27.0	20 257	91.6	<0.001	8183	81.5	8169	81.4	0.80
Mental disorders	28 268	52.5	14 908	47.0	13 360	60.4	<0.001	5798	57.8	5767	57.5	0.66
Alcohol-related illness	5107	9.48	2859	9.01	2248	10.2	<0.001	1061	10.6	942	9.39	0.01
Chronic kidney disease	4601	8.54	1448	4.56	3153	14.3	<0.001	877	8.74	850	8.47	0.50
Gout	11 362	21.1	4444	14.0	6918	31.3	<0.001	2599	25.9	2509	25.0	0.14
Coronary artery disease	17 468	32.4	6395	20.2	11 073	50.1	<0.001	3705	36.9	3749	37.4	0.52
Stroke	6287	11.7	2331	7.34	3956	17.9	<0.001	1169	11.7	1103	11.0	0.14
Medication												
Inhaled corticosteroids	2601	4.83	1340	4.22	1261	5.70	<0.001	499	4.97	475	4.73	0.43
Oral steroids	28 183	52.3	15 080	47.5	13 103	59.2	<0.001	5461	54.4	5503	54.8	0.55

χ^2 test.
*t-test.

haematological malignancy (aHR=0.47; 95% CI 0.30 to 0.73), head and neck cancer (aHR=0.40; 95% CI 0.18 to 0.87), liver cancer (aHR=0.22; 95% CI 0.15 to 0.30), pancreatic cancer (aHR=0.53; 95% CI 0.30 to 0.94) and other immunological cancers (aHR=0.29; 95% CI 0.22 to 0.37) (table 3).

Our age-stratified analysis demonstrated that statin use was significantly associated with a lower risk for all cancers among patients aged ≥50 years. However, among patients aged ≤49 years, statin use was only associated with lower risk for haematological malignancy (aHR=0.33; 95% CI 0.13 to 0.87), head and neck cancer (aHR=0.40; 95% CI 0.24 to 0.65), other immunological cancers (aHR=0.30; 95% CI 0.18 to 0.50) and kidney cancer (aHR=0.33; 95% CI 0.11 to 0.97) (table 4).

Analysis of the data stratified by follow-up time revealed that most cancers developed within the first 0.5 years. The follow-up periods of 0.5–1 year, 1–2 years and >2 years were associated with a lower risk for all cancers. The application of the multivariable adjusted Cox proportional hazards model revealed that relative to statin non-users, statin users exhibited a significantly lower risk for cancer during the follow-up periods (table 5).

Time-dependent covariates in propensity score-matched sensitivity analysis

Table 6 presents the sensitivity analysis for propensity-matched statin users and non-users. Our results for the association between statin use and risk of cancer are similar to the key findings reported by other studies (table 2). In the matched cohorts, statin users exhibited significantly lower risk for all cancers (aHR=0.60; 95% CI 0.55 to 0.65), haematological malignancy (aHR=0.52; 95% CI 0.35 to 0.78), head and neck cancer (aHR=0.52; 95% CI 0.38 to 0.72), colorectal cancer (aHR=0.73; 95% CI 0.59 to 0.89), liver cancer (aHR=0.34; 95% CI 0.26 to 0.43), pancreatic cancer (aHR=0.39; 95% CI 0.23 to 0.67), skin cancer (aHR=0.40; 95% CI 0.17 to 0.96), breast cancer (aHR=0.67; 95% CI 0.52 to 0.87), other immunological cancers (aHR=0.37; 95% CI 0.30 to 0.46), cervical cancer (aHR=0.27; 95% CI 0.14 to 0.54), kidney cancer (aHR=0.73; 95% CI 0.54 to 0.98) and other

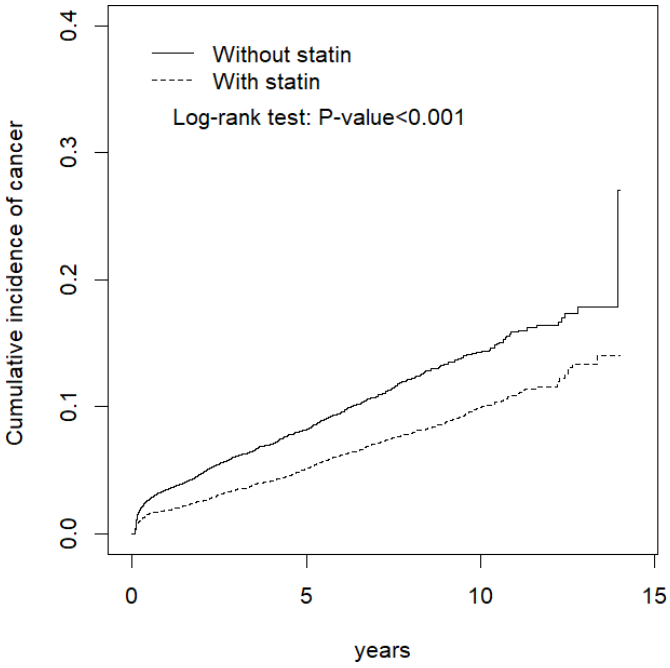

Figure 1 Cumulative incidence of cancer was lower in statin users than in non-statin controls.

cancers (aHR=0.62; 95% CI 0.44 to 0.88). No association between statin use and risk for lung cancer was observed (aHR=0.88; 95% CI 0.71 to 1.09).

DISCUSSION

The first major finding of the present study was that relative to patients with ILD and pulmonary fibrosis who did not take statins, those who took statins exhibited a lower risk for cancers such as colorectal cancer, liver cancer, breast cancer, Hodgkin's lymphoma and Kaposi's sarcoma.[25] These cancers are associated with the overexpression of cytokines (such as IL-6), ACE activity, EGFR, vascular endothelial growth factor (VEGF) and MMPs and are regarded as immunological cancers.[3–6] The axis formed by ACE2 is a potent counter-regulator against ACE activity.[33 34] Statins may play an auxiliary role in enhancing the ability of ACE2 to correct the imbalance of ACE/ACE2, inhibit IL-6 activity, and attenuate the activity of EGFR, VEGF and MMPs. Thus, patients with ILD and pulmonary fibrosis who use statins exhibit a lower risk for cancer formation (relative to statin non-users), even in the presence of virus infections (see online supplemental figure).[33–35]

In the present study, patients with ILD and pulmonary fibrosis who used statins exhibited a high prevalence of obesity-related diseases such as mental disorder (60.4%), hyperlipidaemia (91.6%), hypertension (80.0%) and coronary artery disease (50.1%).[20 36] These comorbidities aggravated the overexpression of EGFR signalling and VEGF, which are associated with cancer formation among patients with ILD and pulmonary fibrosis.[18 22] Statin use may play an auxiliary role in enhancing the effect of angiotensin 1–7, correction of ACE/ACE2 imbalance, and inhibition of the EGFR and VEGF transactivation through a Mas receptor-dependent pathway.[18 19] These findings suggest that statin use is associated with a lower risk of cancer in patients with ILD and progressive pulmonary fibrosis, particularly when they also have the aforementioned comorbidities.[25 36–39]

Nielsen *et al*[40] reported that patients who used statins (regardless of whether their daily dose level was low, moderate or high) exhibited a lower aHR for cancer-related mortality compared with those who did not use statins. The low aHRs for cancer-related mortality that were associated with the <0.5 year and 0.5–1 year follow-up periods among statin users suggest that early statin use (ie, within 1 year after diagnosis of ILD) is associated with a lower risk of cancer among patients with ILD. A low aHR for cancer-related mortality was also observed in the >2-year follow-up period. A meta-analysis reported that for follow-up periods from 2.5 to 10.7 years, statin use was independently associated with a lower risk of liver cancer in patients with HBV or HCV infection that was related to ILD and pulmonary fibrosis; these results are consistent with those reported in our study.[41] Another large-scale study compared the use of statins among 29 498 patients with colorectal cancer and discovered that statin use at the time of cancer diagnosis is associated with enhanced overall survival. The benefit of statin use appears to persist regardless of cancer stage, location and presence of other cardiovascular comorbidities.[42] A novel finding of our study was that relative to the other follow-up periods, a higher number of cancer incidents occurred within 6 months of ILD and pulmonary fibrosis diagnosis. Notably, relative to the patients with ILD and pulmonary fibrosis who did not use statins, those who used statins exhibited a lower aHR for cancer incidence.

These findings highlight the benefits of early statin use for patients with ILD and pulmonary fibrosis who also have comorbidities such as obesity-related diseases. Statins may play an auxiliary role in attenuating the risk of haematological malignancy, head and neck cancer, colorectal cancer, liver cancer, pancreatic cancer and breast cancer, which are associated with obesity among patients with ILD and pulmonary fibrosis who are aged ≥50 years. For example, the prevalence of hyperlipidaemia reached 91.6% in patients with ILD and pulmonary fibrosis who were statin users. Statin use reduced low-density lipoprotein cholesterol (LDL-C) levels, increased high-density lipoprotein cholesterol (HDL-C) levels and attenuated the incidence of obesity-related diseases, all of which contributed to the lower risk of cancer among statin users relative to statin non-users. A previous study reported that lower LDL-C and higher HDL-C levels were associated with a lower risk of cancer, which is consistent with our findings.[36 43] However, young adult patients used statins less frequently (compared with patients from other age groups) because they made fewer

Table 2 Overall incidence of cancer (per 1000 person-years) and estimated HR in patients with interstitial lung disease with statin compared with patients with interstitial lung disease and pulmonary fibrosis without statin by Cox proportional hazard model with time-dependent covariates in non-matched cohorts

	Statin					
	No (n=31 738)		Yes (n=22 124)			
Site of cancer	Case	Rate†	Case	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
All cancers	3652	24.2	2031	17.5	0.76 (0.72 to 0.80)***	0.59 (0.55 to 0.63)***
Haematological malignancy	186	1.23	95	0.82	0.69 (0.54 to 0.88)**	0.59 (0.43 to 0.81)***
Head and neck cancer	271	1.80	132	1.14	0.66 (0.54 to 0.82)***	0.55 (0.43 to 0.71)***
Oesophagus	58	0.38	35	0.30	0.81 (0.53 to 1.23)	0.65 (0.39 to 1.09)
Stomach	197	1.31	128	1.10	0.88 (0.70 to 1.10)	0.85 (0.64 to 1.14)
Colon, rectum	562	3.73	407	3.51	0.98 (0.87 to 1.12)	0.78 (0.67 to 0.92)**
Liver	550	3.65	184	1.59	0.45 (0.38 to 0.53)***	0.30 (0.25 to 0.36)***
Pancreas	78	0.52	51	0.44	0.89 (0.62 to 1.26)	0.42 (0.28 to 0.63)***
Lung	455	3.02	333	2.87	0.99 (0.86 to 1.14)	0.80 (0.67 to 0.96)*
Skin	37	0.25	33	0.28	1.19 (0.75 to 1.91)	0.74 (0.42 to 1.31)
Breast cancer	394	4.53	201	3.06	0.70 (0.59 to 0.83)***	0.62 (0.50 to 0.78)***
Other immunological cancers	754	5.00	280	2.41	0.50 (0.44 to 0.57)***	0.35 (0.29 to 0.41)***
Cervix	90	1.04	35	0.53	0.54 (0.37 to 0.80)**	0.33 (0.21 to 0.53)***
Endometrium	58	0.67	44	0.67	1.05 (0.71 to 1.56)	0.72 (0.44 to 1.18)
Ovary	55	0.63	23	0.35	0.58 (0.36 to 0.95)*	0.86 (0.44 to 1.68)
Prostate	178	2.79	130	2.58	0.96 (0.76 to 1.20)	0.83 (0.63 to 1.09)
Bladder, kidney	224	1.49	189	1.63	1.13 (0.93 to 1.38)	0.75 (0.59 to 0.96)*
Brain	34	0.23	19	0.16	0.76 (0.44 to 1.34)	1.27 (0.59 to 2.76)
Thyroid	85	0.56	40	0.34	0.63 (0.43 to 0.92)*	0.67 (0.41 to 1.10)
Others	242	1.60	125	1.08	0.70 (0.56 to 0.87)**	0.61 (0.46 to 0.80)***

*P<0.05, **P<0.01, ***P<0.001.
†Rate, incidence rate, per 1000 person-years; crude HR, relative HR.
‡Adjusting for age, gender, comorbidity of sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illness, chronic kidney disease, gout, CAD and stroke, and ICS and OS medication.
CAD, coronary artery disease; ICS, inhaled corticosteroids; OS, oral steroids.

medical visits; thus, this group of patients did not take sufficient dose of statin to achieve the auxiliary attenuation effect of statins on cancer incidence. Consequently, patients aged ≤49 years who used statin did not exhibit a lower risk for colorectal, pancreatic and lung cancer.

It is important to note that COPD in smokers is associated with risk of pulmonary fibrosis and cancer. ICS, OS and statins[44] play crucial roles in COPD exacerbation and pulmonary fibrosis.[44 45] In the present study, the association of these three drugs with risk of cancer incidence was examined, and we discovered that statin use was independently associated with risk of cancer in the ILD and pulmonary fibrosis cohort.

Our results suggest that statin use played an auxiliary role in reducing cancer incidence among patients with ILD and pulmonary fibrosis. Notably, our study revealed that statin use led to a lower risk of cancer in the <0.5 year, 0.5–1 year and >1 year follow-up periods. These findings should be further verified through prospective randomised trials.

Strengths

First, this was a large-scale study aimed at detecting risk of cancer, particularly risk of immunological cancers, among patients in the general population who have ILD and pulmonary fibrosis. Second, we performed propensity score matching to avoid introducing baseline bias. Third, we conducted a time-dependent analysis to eliminate immortal time bias. Fourth, we stratified the follow-up time into periods of <0.5, 0.5–1, 1–2, 2–3 and ≥3 years to avoid introducing lag-time bias. Fifth, we stratified individuals by age, sex and cancer type to validate our results, and we discovered that the risk for most cancers such as immunological cancers was lower in the statin user group, which was in line with the primary outcome. Sixth, we replaced the lifestyle variable with associated comorbidities. For example, hypertension and

Table 3 Cox proportional hazard model with time-dependent covariates with HR and 95% CI of type of cancer associated with statin stratified by sex among patients with interstitial lung disease and pulmonary fibrosis in non-matched cohorts

	Male with statin		Female with statin	
	No (n=12 228)	Yes (n=9896)	No (n=17 784)	Yes (n=13 954)
Site of cancer	Adjusted HR† (95% CI)		Adjusted HR† (95% CI)	
All cancers	1 (reference)	0.61 (0.56 to 0.67)***	1 (reference)	0.56 (0.51 to 0.62)***
Haematological malignancy	1 (reference)	0.73 (0.47 to 1.14)	1 (reference)	0.47 (0.30 to 0.73)***
Head and neck cancer	1 (reference)	0.57 (0.44 to 0.75)***	1 (reference)	0.40 (0.18 to 0.87)*
Colon, rectum	1 (reference)	0.70 (0.56 to 0.87)**	1 (reference)	0.87 (0.69 to 1.11)
Liver	1 (reference)	0.36 (0.28 to 0.45)***	1 (reference)	0.22 (0.15 to 0.30)***
Pancreas	1 (reference)	0.31 (0.17 to 0.58)***	1 (reference)	0.53 (0.30 to 0.94)*
Lung	1 (reference)	0.82 (0.65 to 1.03)	1 (reference)	0.76 (0.58 to 1.00)
Other immunological cancers	1 (reference)	0.40 (0.33 to 0.50)***	1 (reference)	0.29 (0.22 to 0.37)***
Bladder, kidney	1 (reference)	0.74 (0.53 to 1.02)	1 (reference)	0.76 (0.53 to 1.10)

*P<0.05, **P<0.01, ***P<0.001.
†Adjusted HR: multivariable analysis including age, gender, comorbidity of sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illness, chronic kidney disease, gout, CAD and stroke, and ICS and OS medication.
CAD, coronary artery disease; ICS, inhaled corticosteroids; OS, oral steroids.

alcohol-related illnesses replaced obesity, hyperlipidaemia replaced exercise and obesity, gout replaced diet, stroke replaced air pollution, sleep disorder replaced occupation, mental disorder replaced economic condition, and ICS and OS use replaced smoking-related diseases such as COPD (in Taiwan, up to 82.9% of patients with COPD are smokers) or COPD with asthma (78.1% and 25.6% of such patients received OS and ICS, respectively).[32] We tracked the patients in Taiwan with ILD and pulmonary fibrosis and obtained data relating to their IL-6, ACE, ACE2, angiotensin 1–7, epidermal growth factor, VEGF, CXR and CT results.[46 47] Furthermore, the coronavirus and cancers hijack the same parts of human cells to spread; therefore, this study suggests the potential of using statins to manage cancers associated with virus infections in patients with ILD and pulmonary fibrosis.

Limitations

In this study, not all drugs used for ILD treatment, such as hydroxychloroquine, interferon, anti-interleukin, azathioprine and non-steroidal anti-inflammatory drugs, were analysed. Moreover, the NHIRD does not provide cytokine data. However, in Taiwan, biochemistry data

Table 4 Cox proportional hazard model with time-dependent covariates with HR and 95% CI of type of cancer associated with statin stratified by age among patients with interstitial lung disease and pulmonary fibrosis in non-matched cohorts

	Age ≤49 years		Age ≥50 years	
	Statin		Statin	
	No (n=15 715)	Yes (n=4143)	No (n=16 023)	Yes (n=17 981)
Site of cancer	Adjusted HR† (95% CI)		Adjusted HR† (95% CI)	
All cancers	1 (reference)	0.46 (0.37 to 0.57)***	1 (reference)	0.58 (0.54 to 0.62)***
Haematological malignancy	1 (reference)	0.33 (0.13 to 0.87)*	1 (reference)	0.60 (0.43 to 0.83)**
Head and neck cancer	1 (reference)	0.40 (0.24 to 0.65)***	1 (reference)	0.56 (0.41 to 0.75)***
Colon, rectum	1 (reference)	0.65 (0.34 to 1.25)	1 (reference)	0.75 (0.64 to 0.89)***
Liver	1 (reference)	0.33 (0.17 to 0.63)***	1 (reference)	0.28 (0.23 to 0.34)***
Pancreas	1 (reference)	0.28 (0.02 to 3.50)	1 (reference)	0.40 (0.26 to 0.61)***
Lung	1 (reference)	1.06 (0.53 to 2.12)	1 (reference)	0.75 (0.63 to 0.90)**
Other immunological cancers	1 (reference)	0.30 (0.18 to 0.50)***	1 (reference)	0.33 (0.28 to 0.39)***
Bladder, kidney	1 (reference)	0.33 (0.11 to 0.97)*	1 (reference)	0.74 (0.58 to 0.95)*

*P<0.05, **P<0.01, ***P<0.001.
†Adjusted HR: multivariable analysis including age, gender, comorbidity of sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illness, chronic kidney disease, gout, CAD and stroke, and ICS and OS medication.
CAD, coronary artery disease; ICS, inhaled corticosteroids; OS, oral steroids.

Table 5 Incidence and HR of cancer between subjects with and without statin among patients with interstitial lung disease and pulmonary fibrosis in non-matched cohorts using Cox proportional hazard model

Follow-up years	Statin							
	No			Yes				
	Event	PY	Rate†	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
<0.5	2331	14544	160.3	1035	10454	99.0	0.63 (0.58 to 0.67)***	0.56 (0.51 to 0.61)***
0.5–1	168	14085	11.9	85	10218	8.32	0.70 (0.54 to 0.91)**	0.46 (0.33 to 0.62)***
1–2	245	25831	9.48	154	18991	8.11	0.86 (0.70 to 1.05)	0.54 (0.43 to 0.70)***
2–3	212	21936	9.66	143	16461	8.69	0.90 (0.73 to 1.11)	0.56 (0.43 to 0.73)***
≥3	696	74400	9.35	614	59942	10.2	1.09 (0.98 to 1.22)	0.69 (0.60 to 0.79)***

**P<0.01, ***P<0.001.
†Rate, incidence rate, per 1000 person-years; crude HR, relative HR.
‡Adjusting for age, gender, comorbidity of sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illness, chronic kidney disease, gout, CAD and stroke, and ICS and OS medication.
CAD, coronary artery disease; ICS, inhaled corticosteroids; OS, oral steroids; PY, person-years.

(eg, IL-6 and C reactive protein levels) are tracked in many institutes during the course of ILD and pulmonary fibrosis to monitor drug use for immunodeficiency diseases.[47 48] Cancer and ILD with respiratory failure are categorised as catastrophic diseases.[49] These strict policies help explain the lack of biochemistry data in the NHIRD.

Table 6 Overall incidence of cancer (per 1000 person-years) and estimated HR in patients with interstitial lung disease and pulmonary fibrosis with statin compared with patients with interstitial lung disease and pulmonary fibrosis without statin by Cox proportional hazard model with time-dependent covariates in propensity score-matched sensitivity analysis

Site of cancer	Statin					
	No (n=10036)		Yes (n=10036)			
	Case	Rate†	Case	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
All cancers	1438	30.4	924	17.4	0.60 (0.55 to 0.65)***	0.60 (0.55 to 0.65)***
Haematological malignancy	68	1.44	39	0.74	0.53 (0.36 to 0.79)**	0.52 (0.35 to 0.78)**
Head and neck cancer	109	2.30	60	1.13	0.52 (0.38 to 0.71)***	0.52 (0.38 to 0.72)***
Oesophagus	21	0.44	19	0.36	0.84 (0.45 to 1.57)	0.87 (0.46 to 1.62)
Stomach	62	1.31	64	1.21	0.96 (0.68 to 1.36)	0.98 (0.69 to 1.39)
Colon, rectum	215	4.54	165	3.11	0.72 (0.59 to 0.88)**	0.73 (0.59 to 0.89)**
Liver	245	5.17	88	1.66	0.33 (0.26 to 0.42)***	034 (0.26 to 0.43)***
Pancreas	45	0.95	19	0.36	0.39 (0.23 to 0.67)***	0.39 (0.23 to 0.67)***
Lung	174	3.67	160	3.02	0.86 (0.69 to 1.06)	0.88 (0.71 to 1.09)
Skin	18	0.38	7	0.13	0.37 (0.15 to 0.88)*	0.40 (0.17 to 0.96)*
Breast cancer	134	5.24	100	3.41	0.68 (0.53 to 0.89)**	0.67 (0.52 to 0.87)**
Other immunological cancers	322	6.80	130	2.45	0.37 (0.30 to 0.46)***	0.37 (0.30 to 0.46)***
Cervix	36	1.41	11	0.38	0.28 (0.14 to 0.55)***	0.27 (0.14 to 0.54)***
Endometrium	30	1.17	22	0.75	0.67 (0.39 to 1.17)	0.67 (0.38 to 1.16)
Ovary	13	0.51	14	0.48	0.99 (0.47 to 2.11)	1.00 (0.47 to 2.13)
Prostate	80	3.67	63	2.66	0.76 (0.54 to 1.05)	0.82 (0.59 to 1.15)
Bladder, kidney	100	2.11	77	1.45	0.72 (0.53 to 0.97)*	0.73 (0.54 to 0.98)*
Brain	8	0.17	9	0.17	1.05 (0.41 to 2.72)	1.02 (0.39 to 2.66)
Thyroid	29	0.61	21	0.40	0.68 (0.39 to 1.18)	0.67 (0.38 to 1.17)
Others	80	1.69	54	1.02	0.63 (0.45 to 0.89)**	0.62 (0.44 to 0.88)**

*P<0.05, **P<0.01, ***P<0.001.
†Rate, incidence rate, per 1000 person-years; crude HR, relative HR.
‡Adjusting for age, gender, comorbidity of sleep disorder, diabetes, hypertension, hyperlipidaemia, mental disorders, alcohol-related illness, chronic kidney disease, gout, CAD and stroke, and ICS and OS medication.
CAD, coronary artery disease; ICS, inhaled corticosteroids; OS, oral steroids.

The NHIRD also does not provide pathological and CT data. However, in Taiwan, ILD is generally diagnosed through CT and pathology tests.[28] Another limitation of the present study is that we did not stratify the statins into lipophilic and hydrophilic statins for sensitivity analysis. A previous NHIRD study reported that lipophilic and hydrophilic statins can aid in the attenuation of risk of cancer.[50] The comparison of a randomised control study, reverse causation, adjustments for causal intermediaries and depletion of susceptibles were the limitations of the aforementioned observational study. For example, statin use did not influence the risk of oesophageal, stomach, endometrial, ovarian, prostate, brain or thyroid cancer. One explanation is that observational studies that used the ICD-9-CM were unable to collect and adjust data relating to diet, exercise, socioeconomic status, smoking status, vitamin supplementation, and screening history for oesophageal, stomach, endometrial, ovarian, prostate, brain and thyroid cancer, all of which are potential confounders for the effect of statins on these cancers. Furthermore, the current cohort did not exhibit a particularly high incidence of lung cancer, which may be explained by the high proportion of patients with mild-stage ILD. This is another limitation of the present study.

CONCLUSION

Statin use is associated with a lower risk of cancer incidence in those with ILD and pulmonary fibrosis.

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