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The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK

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Summary
Background: The aim of this study was to use a longitudinal computerised health care dataset (The Health Improvement Network) to provide information on the overall incidence of cancer, and on the incidence of organ-specific cancers, in people with idiopathic pulmonary fibrosis (IPF) and sarcoidosis in comparison to the general population.
Methods: Incident cases of IPF and sarcoidosis were identified with up to four controls matched by age, gender and general practice. Cancer incidence rates were compared between cohorts using Cox regression and adjusting for age, gender and smoking habit.
Results: One thousand and sixty-four incident cases of IPF (mean age at diagnosis 71.5 years; 62.4% male) were identified. Overall, the incidence of cancer was increased in people with IPF compared to the general population (rate ratio 1.51; 95% CI 1.20–1.90), but this was largely due to a marked increase in the incidence of lung cancer (rate ratio 4.96; 95% CI 3.00–8.18). One thousand one hundred and fifty-three incident cases of sarcoidosis (mean age at diagnosis 47.0 years; 47.2% male) were identified. There was an overall increased incidence of cancer in sarcoidosis (rate ratio 1.65; 95% CI 1.22–2.24) and this was largely explained by an increase in the incidence of skin cancers (rate ratio 1.86; 95% CI 1.11–3.11).
Conclusions: This study provides further evidence of a marked increase in the incidence of lung cancer in people with IPF, but we found no increase in the risk of other cancers. People with sarcoidosis did have an increase risk of skin cancers, but not cancers at other sites.

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Introduction

The possible association between idiopathic pulmonary fibrosis (IPF) and lung cancer was first noted in a series of cases described over 30 years ago.[1] Three large epidemiological studies have subsequently investigated this association with conflicting results. The first study reported a relative risk of lung cancer of 14.1 in patients with IPF compared to the general population.[2] These findings were not supported by the second study, however, which used death certificates to investigate the frequency of recording of lung cancer for people with fibrosing alveolitis compared to coal-workers pneumoconiosis and silicosis.[3] A more recent cohort study used computerised primary care data from the UK and demonstrated an increase in the risk of lung cancer in patients with IPF of a similar magnitude to that seen by Turner-Warwick et al.[2,4] No studies have examined the incidence of cancer at other sites in patients with IPF.

Early studies of patients with sarcoidosis suggested a possible association with malignancy, particularly lymphoma and lung cancer.[5–7] Two Danish studies have investigated the incidence of cancer in hospital-based cohorts of people with sarcoidosis, using national cancer statistics for the general population as the comparator.[8,9] Both found small increases in cancer incidence in people with sarcoidosis which were not significant at the 5% level. More recently, a larger study has compared the incidence of cancer in a cohort of people with sarcoidosis derived from the Swedish inpatient registry to national data and found a small increase in the risk of cancer overall, together with specific increases in stomach, small intestine, large intestine and skin cancer and also lymphoma and leukaemia.[10] The main limitation of all of these studies is that the comparator data are drawn from national statistics and so no allowance can be made for confounders acting at the individual level, such as smoking habit.

The aims of this paper were to provide more accurate information on the incidence of lung cancer in patients with IPF, to perform a systematic examination of cancers at other sites in patients with IPF and to study the putative association between sarcoidosis and malignancy.

Methods

The Health Improvement Network (THIN) is a longitudinal primary care dataset, which includes diagnostic and prescription data collected as part of routine primary care in the UK.[11] The version of THIN used in this study includes information collected up to November 2004 by 255 primary care centres. Each person in THIN has a start date, defined as the later of their date of registration or practice date of computerisation, and a stop date defined as the earliest of date of death or last data collection.

For this study we analysed data from two patient cohorts, one containing people with IPF and one with people with sarcoidosis and two matched general population control cohorts.

People were included in the IPF cohort if they had at least one recorded IPF diagnosis and their first IPF diagnosis was recorded at least 12 months after their start date at initial diagnosis. This strategy was designed to capture incident rather than prevalent cases. Those with connective tissue diseases and under the age of 40 were excluded from the dataset to increase the diagnostic specificity. A control cohort consisting of up to four general population controls per IPF patient, matched by age, gender and general practice was selected. An index date, defined as the earliest recorded diagnosis of IPF for the cases and the same date for the matched controls, was assigned to each study participant. All of the controls were contributing data at the time of the index data. For each case and control, we extracted information on smoking habit throughout the data record and diagnoses of cancer after the index date.

Similar methods were used to identify a cohort of people with sarcoidosis and a matched control cohort, though for these analyses no age restrictions were applied.

We extracted data on smoking habit for all study participants and recoded these data as non/never, current or ex-smokers or missing. Where data permitted, current smokers were divided into groups who smoked <10, 10–19 and $\geqslant 20$ per day. We estimated the association between smoking habit and diagnoses of IPF or sarcoidosis in comparison to general population controls using conditional logistic regression.

In order to compare the incidence of cancer between cases and controls, we initially calculated the crude cancer rates, and then used multivariate Cox regression models to compare cohorts and allow for the possible confounding effects of age, gender and smoking habit. Initially time to any malignancy was analysed, then the times to following subsets of: any malignancy excluding non-melanomatous skin cancer (NMSC), skin cancers, lung cancer, prostate cancer (in men), gastrointestinal cancers, breast cancer (in women), leukaemia, lymphoma, gynaecological cancers (in women), ear, nose and throat (ENT) cancers, renal cancers and liver cancers were explored individually. In the analyses of cancer incidence the start of follow-up was defined as the index date, and the finish date was either the date of a cancer diagnosis or the date of last data collection, whichever came first. Evidence of an effect modification by age, gender and smoking habit was assessed by fitting multiplicative interaction terms, and proportional hazard assumptions were checked using a combination of the diagnostic section within STATA (stsphtest in version 8, STATA Corporation, Texas) and log–log plots. Likelihood ratio tests were used for all hypothesis tests. STATA version 8 was used for all of the statistical analyses and likelihood ratio tests.

The study protocol was reviewed and approved by the Nottingham Research Ethics Committee.

Results

A total of 1064 incident cases of IPF were identified. The mean age at diagnosis was 71.5 years (S.D. 10.6 years) and 62.4% were male. The total number of person-years of follow-up after the diagnosis of IPF was 2598 years (mean 2.4 years). A total of 4238 matched controls (3.98 per case) were identified. The mean age of the controls at their matched diagnosis date was 71.5 years (S.D. 10.6 years) and 62.4% were male. The total follow-up time for the IPF control cohort was 15,294 person-years (mean 3.6 years).

People with IPF were marginally more likely to be a current or ex-smokers than controls but these effects were not significant at the 5% level, and no dose–response relationship was apparent (Table 1).

The absolute numbers of diagnoses for all cancers and cancers at specific sites for people with IPF and their matched controls are given in Table 2 along with rate per 10,000 person-years, and both age and gender, and age, gender and smoking status adjusted rate ratios with 95% confidence intervals. No further analysis was carried out in the categories where no cases of cancer were found in either the IPF cohort or their controls. During the period of study follow-up, 93 people with IPF and 371 controls were diagnosed with at least one malignancy. There was a small but significant increase in ''all cancers'' when adjusted for age, gender and smoking habit (rate ratio 1.51; 95% confidence intervals 1.20–1.90). Our specific site analysis demonstrated a marked increase in the incidence of lung cancer in patients with IPF compared to the general population (rate ratio 4.96; 95% confidence intervals 3.00–8.18), but no statistically significant increases at other sites.

One thousand one hundred and fifty-three incident cases of sarcoidosis were identified. Their mean age at diagnosis was 47.0 years (S.D. 13.9 years) and 47.2% were male. The total number of person-years of follow-up after the index diagnosis of sarcoidosis was 6083 (mean 5.3 years). A total of 4610 controls (4.0 per case) were identified. The mean age of the controls at their matched diagnosis date was 47.0 years (S.D. 13.9 years) and 47.2% were male. The total follow-up time for the sarcoidosis control cohort was 23,746 person-years (mean 5.2 years). People with sarcoidosis were less likely to be current smokers than their matched controls (odds ratio of 0.53; 95% confidence intervals 0.45–0.63) and the protective effect of smoking did seem to be dose-related (Table 3).

The absolute numbers of diagnoses for all cancers and cancers at specific sites for people with sarcoidosis and their matched controls are given in Table 4 along with rate per 10,000 person-years, and both age and gender, and age, gender and smoking status adjusted hazard ratios with 95% confidence intervals. During the period of study follow-up, 58 people with sarcoidosis and 161 controls were diagnosed with at least one malignancy. This produced a 53% relative increase in risk among people with sarcoidosis (rate ratio of 1.53; 95% confidence interval 1.13–2.07) when adjusted for age and gender. This effect increased further (rate ratio 1.65; 95% confidence interval 1.22–2.24) after adjusting for smoking status. An increase of similar magnitude was seen for skin cancers when adjusted for age, gender and smoking status (rate ratio 1.86; 95% confidence interval 1.11–3.11). The age, gender and smoking habit adjusted relative risk of lymphoma showed the most marked increase (rate ratio 7.04; 95% confidence interval 1.54–32.1). None of the other cancers at specific sites demonstrated a difference in incidence in sarcoidosis at the 95% level.

We found no evidence that the proportional hazards assumptions for our final models were incorrect.

Discussion

In a large cohort of people with IPF, we found a small increase in cancer incidence overall compared to the general population, largely accounted for by a marked increase in the incidence of lung cancer. There was no significant risk of cancers at other sites. In our cohort of people with sarcoidosis we also found a small relative increase in the incidence of cancer which due almost entirely to an increase in the incidence of skin cancers.

Strengths and weaknesses of the study

The main strengths of our study are the large size of our cohorts, the presence of an appropriate internal general population control group, and the availability of data on an individual basis to allow us to control for smoking habit. In addition the duration of follow-up, though limited by poor median survival in IPF, was sufficient to allow us to examine reasonable absolute numbers of cancer diagnoses.

The main potential weakness of our study is the validity of the IPF, sarcoidosis and cancer diagnoses. In general, the

Table 1 Association between smoking habit and IPF.

Smoking status/ amount	Cases (*n* (%))	Controls (*n* (%))	Odds ratio (95% confidence interval)	*p*-Value for trend
Smoking status				
Non	398 (43%)	1670 (47%)	1	
Current	284 (31%)	1043 (29%)	1.17 (0.98–1.41)	
Ex	240 (26%)	858 (24%)	1.21 (1.00–1.46)	
Missing	142	667	–	
Total with smoking status data = 4493 (84.7%)				
Cigarettes per day				
Non	398 (37.4%)	1670 (39.4%)	1	
<10	50 (4.7%)	164 (3.9%)	1.31 (0.93–1.84)	0.712
10–19	50 (4.7%)	199 (4.7%)	1.08 (0.77–1.51)	
⩾20	56 (5.3%)	217 (5.1%)	1.11 (0.80–1.54)	
Number of current smokers with data on amount smoked = 736 (55.5%)				

Table 2 Diagnoses of cancer in incident IPF.

Condition and cohort	Number of events	Rate per 10,000 person-years	Rate ratio* (95% confidence interval)	Rate ratio† (95% confidence interval)
All malignancies				
Control	371	254	1.51	1.51
IPF	93	373	(1.20–1.90)	(1.20–1.90)
All malignancies except NMSC				
Control	300	203	1.57	1.58
IPF	79	311	(1.23–2.02)	(1.23–2.03)
Skin cancers				
Control	93	61.7	1.09	1.08
IPF	16	62.6	(0.64–1.85)	(0.63–1.84)
Lung cancer				
Control	35	22.9	4.99	4.96
IPF	29	112	(3.03–8.22)	(3.00–8.18)
Prostate cancer				
Control	47	52.2	1.08	1.09
IPF	8	54.4	(0.51–2.30)	(0.51–2.32)
Gastrointestinal cancer				
Control	47	30.9	0.84	0.86
IPF	6	23.1	(0.36–1.97)	(0.37–2.03)
Breast cancer				
Control	23	37.5	1.23	1.17
IPF	5	45.5	(0.47–3.26)	(0.44–3.10)
Leukaemia				
Control	10	6.54	0.63	0.63
IPF	1	3.85	(0.08–5.01)	(0.08–5.00)
Lymphoma				
Control	6	3.93	2.48	2.73
IPF	3	11.6	(0.62–9.97)	(0.68–11.1)
Gynaecological cancers				
Control	2	3.23	2.20	2.21
IPF	1	9.04	(0.20–24.3)	(0.20–24.4)
ENT cancers				
Control	5	3.27		
IPF	0			
Renal cancer				
Control	2	1.31		
IPF	0			
Liver cancer				
Control	1	0.65	5.07	8.25
IPF	1	3.85	(0.31–82.5)	(0.48–141)

*Crude rate ratio adjusted for age and gender.
†Rate ratio adjusted for age, gender and smoking habit.

validity of diagnoses in general practice datasets has been found to be high for a wide spectrum of diagnoses.[12] Furthermore, we have previously investigated the validity of the IPF diagnoses in the UK General Practice Research Database (GPRD),[4] a database with similarities and overlap with THIN, and found it to be high. Although the diagnoses of IPF and sarcoidosis have not been specifically validated in THIN, it is unlikely that this dataset differs markedly from the GPRD or that a general practitioner would record these relatively uncommon, specialist diagnoses without confirmation from a referral to secondary care. Evidence supporting this comes from the demographics of the IPF

Table 3 Effect of smoking on the incidence of sarcoidosis.

Smoking status/ amount	Cases (*n* (%))	Controls (*n* (%))	Odds ratio (95% confidence interval)	*p*-Value for trend
Smoking status				
Non	662 (65%)	1966 (54%)	1	
Current	238 (23%)	1256 (34%)	0.53 (0.45–0.63)	
Ex	124 (12%)	444 (12%)	0.82 (0.66–1.03)	
Missing	129	944	–	
Total with smoking status data = 4690 (81.4%)				
Cigarettes per day				
Non	662 (57.4%)	1966 (42.6%)	1	
<10	47 (4.1%)	201 (4.4%)	0.68 (0.49–0.95)	0.0001
10–19	36 (3.1%)	294 (6.4%)	0.35 (0.25–0.51)	
⩾20	40 (3.5%)	332 (7.2%)	0.35 (0.25–0.49)	
Number of current smokers with data on amount smoked = 950 (63.6%)				

and sarcoid datasets that are similar to those published previously.[2–4,13–15] The validity of a range of cancer diagnoses has previously been tested in general practice datasets and been found to be high.[17] Furthermore, the incidence rates of organ-specific cancer diagnoses in our control group are similar to those reported for UK cancer registrations (http://www.statistics.gov.uk/STATBASE).

Smoking data were available for a high percentage of the cases and controls in both datasets, and the proportion of current smokers is consistent with data reported in UK household survey data. The ex-smoker rate is lower than expected,[18] however, and this almost certainly reflects a degree of misclassification of ex-smokers as non-smokers. In a previous study using a computerised general practice database we found a similar misclassification of ex-smokers as non-smokers, but also found that within current smokers the dose–response relationship between number of cigarettes smoked per day and lung cancer risk was entirely as expected suggesting that the data on cigarettes per day have high validity.[4] Currently available data on the effect of cigarette smoking on the incidence of IPF are mixed. Two studies show a small increased risk of IPF in ever-smokers with odds ratios of 1.6,[13,14] but, in common with a number of other studies,[4,19] we found no significant effect. The marginal increase of about 20% in recorded diagnoses of IPF in current and ex-smokers was of a similar magnitude to those demonstrated in our previous large cohort study.[4] Our data also demonstrate that current smokers are half as likely to have a recorded diagnosis of sarcoidosis; this effect is still greater in those people smoking over 10 cigarettes per day. The protective effect of smoking is similar to that seen in other studies[15,16] adding further validity to our diagnoses of sarcoidosis, and providing evidence of a dose-related effect for the first time.

IPF

This study is one of the largest cohort studies of IPF in the absence of connective tissue disease in the literature to date. Analysis of these data provides further evidence that the incidence of lung cancer in IPF is markedly increased compared to the general population and that this effect is independent of smoking status. Increased ascertainment of lung cancers during the diagnosis of and follow-up of people with IPF might explain some of the increase we observed, but given the large magnitude of the increase it seems likely to us that this is entirely explained by ascertainment. The mechanism by which IPF increases the risk of lung cancer is unclear, and though this may relate to the presence of fibrosis it is also possible that other exposures associated with IPF, such as the use of immunosuppressive drugs, may also have a role.

A previous study from our group using the GPRD showed a similar association between IPF and lung cancer (smoking-adjusted RR 8.25; 95% confidence intervals 4.70–11.48).[4] That study followed similar methodology but did not attempt to exclude prevalent cases or to restrict the diagnosis of cancer to those made after the diagnosis of IPF. Post hoc analysis of our data including all cases, incident and prevalent, however, did not appreciably alter the results.

Sarcoidosis

This is the first large cohort study to compare the incidence of cancer in people with sarcoidosis to individuals in the general population and to allow for the impact of smoking habit. Our rate ratio of 1.65 for all cancers is slightly greater than both the two Danish studies which demonstrated trends towards increased cancer incidence with rate ratios of 1.4[9] and 1.2,[8] respectively, and the larger Swedish study which found a significant rate ratio 1.3.[10] This difference is accounted for in part by controlling for smoking habit: as people with sarcoidosis are less likely to smoke than the general population and smoking is an important risk factor for many cancers it is likely that the previous findings underestimated the true association between sarcoidosis and cancer risk.

Our analysis of individual cancer types indicates that the most dramatic increases are in lymphoma (rate ratio 7.08) and the more common skin cancers (rate ratio 1.89). Examination of the absolute differences in incidence rates

Table 4 Diagnoses of cancer in incident sarcoidosis.

Condition and cohort	Number of events	Rate per 10,000 person-years	Rate ratio* (95% confidence interval)	Rate ratio† (95% confidence interval)
All malignancies				
Control	161	69.1	1.53	1.65
Sarcoidosis	58	98.6	(1.13–2.07)	(1.22–2.24)
All malignancies except NMSC				
Control	131	55.9	1.27	1.37
Sarcoidosis	40	67.2	(0.89–1.82)	(0.96–1.96)
Skin cancers				
Control	49	20.8	1.80	1.86
Sarcoidosis	21	35.0	(1.08–3.00)	(1.11–3.11)
Lung cancer				
Control	7	2.95	2.57	3.24
Sarcoidosis	4	6.58	(0.75–8.84)	(0.94–11.2)
Prostate cancer				
Control	9	8.11	0.98	1.00
Sarcoidosis	2	7.15	(0.21–4.56)	(0.21–4.68)
Gastrointestinal cancer				
Control	15	6.32	0.85	0.92
Sarcoidosis	3	4.94	(0.24–2.93)	(0.26–3.22)
Breast cancer				
Control	29	23.3	1.11	1.29
Sarcoidosis	8	24.7	(0.51–2.42)	(0.59–2.85)
Leukaemia				
Control	3	1.26		
Sarcoidosis	0			
Lymphoma				
Control	3	1.26	5.34	7.04
Sarcoidosis	4	6.61	(1.19–23.9)	(1.54–32.1)
Gynaecological cancers				
Control	1	0.79		
Sarcoidosis	0			
ENT cancers				
Control	3	1.26		
Sarcoidosis	0			
Renal cancer				
Control	3	1.26		
Sarcoidosis	0			
Liver cancer				
Control	1	0.42	3.78	2.88
Sarcoidosis	1	1.64	(0.24–60.6)	(0.18–46.3)

*Crude rate ratio adjusted for age and gender.
†Rate ratio adjusted for age, gender and smoking habit.

reveals that an increase in the diagnosis of skin cancers is the most important component of this overall increase in cancer incidence. We were concerned that this increase might represent ascertainment bias due to the visibility of skin lesions and the increased contact with medical practitioners after a diagnosis of sarcoidosis; however, there was no equivalent increase in skin cancers in the IPF cohort. In addition, an increased incidence of skin cancers in sarcoidosis has been reported previously.[10] The increase in lymphoma has also been demonstrated in early case series of patients with sarcoidosis[5–7] and the Askling cohort.[10] The high rate ratio, however, results from small absolute

numbers and we were concerned that the effect could be due to misdiagnosis. Examination of individual cases revealed a time gap of 1.44–3.00 years between the diagnosis of sarcoidosis and subsequent reporting of lymphoma which would be in keeping with the possibility of misdiagnosis.

Summary

Our findings suggest that people with IPF have a markedly increased risk of developing lung cancer. People with IPF should be strongly encouraged to give up smoking and should be offered smoking cessation advice and support as a matter of urgency. Our findings also suggest that people with IPF might represent a suitable population for lung cancer screening. In general, our findings with regard to cancer in people with sarcoidosis are reassuring although further research is required to elucidate the association between sarcoidosis and skin cancer.

Conflict of interest statement

There are no conflicts of interest for any of the authors.

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