SHORT COMMUNICATION

Chronic Obstructive Pulmonary Disease and Risk of Cutaneous T-cell Lymphoma: A Danish Population-based Cohort Study

Sissel B.T. SØRENSEN[1,2], Dávid NAGY[2], Niels ØDUM[3], Lars IVERSEN[1] and Lise M. LINDAHL[1]
[1]Department of Dermatology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark, [2]Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Aarhus and [3]Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark. E-mail: sts@clin.au.dk
Accepted May 9, 2023; Published Aug 23, 2023
Acta Derm Venereol 2023; 103: adv5238. DOI: 10.2340/actadv.v103.5238

Cutaneous T-cell lymphoma (CTCL) is a rare heterogeneous subtype of extranodal non-Hodgkin lymphoma (1). The aetiology of CTCL is largely unknown; however, smoking has been suggested as an aggravating cause (2). A pooled analysis of 324 patients with CTCL and 17,217 controls from 14 different case-control studies showed that prolonged smoking (>40 years) was associated with an increased risk of CTCL (odds ratio (OR) 1.55, 95% confidence interval (95% CI) 1.04–2.31) (2). A multicentre case-control study of 76 cases of mycosis fungoides (MF), the most common form of CTCL, and 2,899 controls reported an almost similar association between heavy smoking and MF (OR 1.30, 95% CI 0.47–1.87) (3), but the risk estimates were imprecise and most compatible with no important effect.

Smoking may promote the pathogenesis of lymphomas, including CTCL, by suppressing and remodelling the immune response (4). The effects of smoking on the immune system include inhibition of cell apoptosis (5), down-regulation of macrophages and natural killer cells, and reduced T-cell response (4). Furthermore, smoking releases substances, such as benzene and formaldehyde that have direct carcinogenic effects (6, 7).

Chronic obstructive pulmonary disease (COPD) is a very common pulmonary disorder, characterized by progressive obstruction of the airways, which most often develops as a consequence of long-term tobacco smoking (8). Thus, COPD can be used as a valid surrogate marker of smoking. This study therefore examined the risk of CTCL in patients with COPD in a large cohort study using Danish health registries.

It is well known that case-control studies, in particular, might be prone to several types of biases in particular recall bias (9). Since CTCL is a very rare disease, it is difficult to find large cohorts of smokers with complete long-term follow-up where CTCL is diagnosed and recorded. Therefore, longitudinal registry-based cohorts may be an alternative.

MATERIALS AND METHODS

This population-based, nationwide cohort study was conducted using data routinely and prospectively collected from Danish population-based registries over the 40-year period between 1978 and 2018. Data were collected from the Danish National Patient Registry (DNPR), the Danish Cancer Registry (DCR), and the Civil Registration System (CRS).

All records were linked at individual level using the unique identification number assigned by the CRS to all legal Danish residents upon birth or immigration. CRS has information on residency status and date of birth, immigration, emigration, and death, and enables accurate record linkage of all Danish health registries at the individual level (10).

Chronic obstructive pulmonary disease cohort

From the DNPR, a cohort of all cancer-free individuals with a first-time hospital-based diagnosis of COPD between 1 January 1978 and 30 November 2018 was identified. The DNPR has data from all Danish inpatient admissions since 1977 and all outpatient specialist clinic and emergency room visits since 1995. Diagnoses are coded using the International Classification of Diseases, Eighth Revision (ICD-8) from 1977 until 1993 and the Tenth Revision (ICD-10) since 1994 (10). The study cohort was restricted to patients older than 20 years at the time of COPD diagnosis.

Cutaneous T-cell lymphoma, non-Hodgkin lymphoma and lung cancer outcomes

The COPD cohort was linked to the DCR to identify incident CTCL overall, and MF (using ICD-10 and/or CTCL morphology codes), non-Hodgkin lymphoma, and lung cancer cases. The DCR has recorded all incident cases of malignant neoplasms in Denmark since 1943. Cancer cases are coded according to the ICD-10 (10). There is no clear evidence that smoking is a risk factor for non-Hodgkin lymphoma (11) in contrast to strong evidence for lung cancer (12). To examine the robustness of the study design, an analysis for these 2 cancer sites was also conducted as a negative and positive control outcome.

Statistical analyses

The COPD cohort was followed from index date until a first-time cancer record in the DCR, death, emigration, or end of follow-up, (30 November, 2018), whichever came first. The first year following COPD diagnosis was excluded to avoid inclusion of prevalent cancers and to reduce the bias from heightened diagnostic efforts associated with multiple hospital contacts. Standardized incidence ratio (SIR) was used as a measure of relative risk, comparing the observed CTCL, non-Hodgkin lymphoma and lung cancer incidences among the COPD cohort to the one expected based on national cancer incidence rates by sex, age, and calendar year. 95% CIs were calculated using Byar's approximation and based on the assumption that the observed number of cancers follows a Poisson distribution.

RESULTS

A total of 363,810 individuals (47.1% women) with a first-time hospital-based diagnosis of COPD between 1978 and 2018 were identified (**Table I**). The median

Table I. Characteristics of study cohort

Characteristics	COPD N = 363,810
Sex	
Female	171,400 (47.1)
Male	192,410 (52.9)
Age, years	
20–29	2,650 (0.7)
30–39	7,662 (2.1)
40–49	23,764 (6.5)
50–59	58,494 (16.1)
60–69	100,627 (27.7)
70+	170,613 (46.9)
Calendar period at COPD diagnosis	
1978–1982	37,683 (10.4)
1983–1987	34,635 (9.5)
1988–1992	30,382 (8.4)
1993–1997	46,847 (12.9)
1998–2002	53,241 (14.7)
2003–2007	51,830 (14.3)
2008–2013	61,479 (16.9)
2014–2018	47,713 (13.1)
Charlson Comorbidity Index (CCI)	
CCI: Low	220,140 (60.5)
CCI: Medium	118,340 (32.5)
CCI: High	25,330 (7.0)
Hospital contact	
Inpatient	253,149 (69.6)
Outpatient	104,203 (28.6)
Emergency room	6,458 (1.8)

COPD: chronic obstructive pulmonary disease.

age of the COPD cohort was 69 years (interquartile range (IQR) 59.8; 76.8) and median follow-up was 4.3 years (IQR 1.42; 9.09). Most patients were initially diagnosed in an inpatient setting (69.6%).

Table II shows the SIRs of all CTCL sybtypes, MF, non-Hodgkin lymphoma, and lung cancer. For more than 1 year of follow-up, 71 patients with COPD received a CTCL diagnosis with a SIR of 1.2 (95% CI 0.9–1.5). Among these, 26 were MF diagnoses, yielding a SIR of 1.6 (95% CI 1.0–2.3).

DISCUSSION

This nationwide large population-based cohort study of 363,810 individuals with COPD did not find any compelling evidence of increased long-term risk of CTCL overall; however, COPD was associated with increased risk of MF. As expected, an elevated risk of lung cancer was found, supporting the robustness of the study design. These results imply that smoking linked to COPD could increase the risk of developing MF, but not other types of CTCL.

Table II. Standardized incidence ratios (SIRs) for cutaneous T-cell lymphoma, mycosis fungoides, non-Hodgkin lymphoma and lung cancer among patients with chronic obstructive pulmonary disease 1978–2018

	≥ 1 year of follow		
	Observed, *n*	Expected, *n*	SIR (95% CI)
Cutaneous T-cell lymphoma	71	62	1.2 (0.9–1.5)
Mycosis fungoides	26	17	1.6 (1.0–2.3)
Non-Hodgkin lymphoma	1,358	1,263	1.1 (1.0–1.1)
Lung, bronchi and trachea cancers	12,966	4,528	2.9 (2.8–2.9)

95% CI: 95% confidence interval.

This study has strengths and limitations. A large nationwide cohort study was conducted, making it possible to investigate rare disease outcomes in a cohort study. Furthermore, the analytic approach is well established and robust within cancer epidemiology (13). Another strength is the usage of Danish health databases that have high completeness and allowing complete long-term follow-up, eliminating the risk of selection bias. Furthermore, both COPD and cancer diagnoses in DNPR and DCR have high accuracy (14). In epidemiological aetiological cancer studies, the first year after diagnosis is often excluded in the analysis to avoid any detection bias due to heightened diagnostic effort.

This study also has some limitations. Although most people with COPD have a history of prolonged exposure to tobacco, up to 20% of patients with COPD may never have smoked (15). Although this could have diluted the relative risk estimates and caused us to underestimate a weak association if such is present, the strong association with lung cancer supports that COPD is an accurate marker of smoking. Therefore, such misclassification probably did not have a substantial impact on the current findings. Furthermore, diagnoses by general practitioners alone are not included in the DNPR, though COPD in these patients might be less severe and associated with a shorter exposure to tobacco.

These findings support some of the findings from the 2 existing case-control studies, which reported similar, but imprecise, risk estimates. Both case-control studies have access to several exposures in addition to smoking.

In conclusion, this large population-based study suggests that COPD, as a marker of excessive smoking, is a risk factor for developing MF, but not other subtypes of CTCL.

Conflicts of interest: LI has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Cilag, Eli Lilly, Janssen-Cilag, Kyowa Kirin, LEO Pharma, MSD, Novartis, Pfizer, Samsung, Sun Pharma and UCB.

REFERENCES

1. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. N Engl J Med 2004; 350: 1978–1988.
2. Aschebrook-Kilfoy B, Cocco P, La Vecchia C, Chang ET, Vajdic CM, Kadin ME, et al. Medical history, lifestyle, family history, and occupational risk factors for mycosis fungoides and Sezary syndrome: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014; 2014: 98–105.
3. Morales Suarez-Varela MM, Olsen J, Kaerlev L, Guenel P, Arveux P, Wingren G, et al. Are alcohol intake and smoking associated with mycosis fungoides? A European multicentre case-control study. Eur J Cancer 2001; 37: 392–397.
4. Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. J Neuroimmunol 1998; 83: 148–156.
5. Wickenden JA, Clarke MC, Rossi AG, Rahman I, Faux SP, Donaldson K, et al. Cigarette smoke prevents apoptosis through inhibition of caspase activation and induces necrosis. Am J Respir Cell Mol Biol 2003; 29: 562–570.
6. Atkinson TJ. A review of the role of benzene metabolites and mechanisms in malignant transformation: summative evidence for a lack of research in nonmyelogenous cancer types. Int J Hyg Environ Health 2009; 212: 1–10.

7. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutation Research/Reviews in Mutation Research 2009; 681: 150–168.
8. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet 2017; 389: 1931–1940.
9. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. Modern epidemiology, 3rd edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia**,** 2008.
10. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019; 11: 563–591.
11. Sergentanis TN, Kanavidis P, Michelakos T, Petridou ET. Cigarette smoking and risk of lymphoma in adults: a comprehensive meta-analysis on Hodgkin and non-Hodgkin disease. Eur J Cancer Prev 2013; 22: 131–150.
12. Freedman ND, Leitzmann MF, Hollenbeck AR, Schatzkin A, Abnet CC. Cigarette smoking and subsequent risk of lung cancer in men and women: analysis of a prospective cohort study. Lancet Oncol 2008; 9: 649–656.
13. Koepsell TD, Weiss NS. Epidemiologic methods: studying the occurrence of illness: Oxford University Press; 2014.
14. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry – history, content, quality and use. Dan Med Bull 1997; 44: 535–539.
15. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. Lancet Respir Med 2013; 1: 543–550.