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Title:
Risk factors for lung cancer in COPD – results from the Bergen COPD Cohort Study

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Key words: COPD, lung cancer, phenotypes, inflammation

Risk factors for lung cancer in COPD – results from the Bergen COPD Cohort Study abstract

Background: COPD patients have an increased risk of developing lung cancer, but the underlying mechanisms are poorly understood. We aimed to identify risk factors for lung cancer in patients from the Bergen COPD Cohort Study.

Methods: We compared 433 COPD patients with 279 healthy controls, all former or current smokers. All COPD patients had FEV1<80% and FEV1/FVC-ratio<0.7. Baseline predictors were sex, age, spirometry, body composition, smoking history, emphysema assessed by CT, chronic bronchitis, prior exacerbation frequency, Charlson Comorbidity Score, inhalation medication and 44 serum/plasma inflammatory biomarkers. Patients were followed up for 9 years recording incidence of lung cancer. Cox-regression models were fitted for the statistical analyses. The biomarkers were evaluated using principal component analysis.

Results: 28 COPD patients and 3 controls developed lung cancer, COPD patients had a significantly higher risk of developing lung cancer, (HR 5.0; 95% CI 1.5-17.1, p<0.01, adjusted values). Among COPD patients, emphysema (HR 4.4; 1.7-10.8, p<0.01) and obesity (HR 3.3; 1.3-8.5, p=0.02) were associated with a higher cancer rate. Use of inhaled steroids was associated with a lower rate (HR 0.4; 0.2-0.9, p=0.03). Smoking status, pack-years smoked or levels of systemic inflammatory markers, except for interferon gamma-induced protein 10, did not affect the lung cancer rate in patients with COPD.

Conclusion: Patients with COPD have a higher lung cancer rate compared to healthy controls adjusted for smoking. The presence of emphysema and obesity in COPD predicted a higher lung cancer risk in COPD patients. Systemic inflammation was not associated with increased lung cancer risk.

Risk factors for lung cancer in COPD – results from the Bergen COPD Cohort Study

Introduction

COPD and lung cancer are two major causes of morbidity and mortality worldwide. COPD is the fourth leading cause of death in the world, whereas lung cancer is the foremost cause of cancer deaths [1]. The incidence of both conditions have been increasing in the last years, and this trend is expected to continue for the next decade [2]. Furthermore, there is a known association between these two common disorders [3]. One obvious explanation for the co-existence of these conditions is their common risk factors, where tobacco-smoking is the most important. However, several studies find that a diagnosis of COPD, regardless of the amount of smoking, is an independent risk factor for development of lung cancer [4,5]. Additionally, lung cancer incidence has been also shown to be associated with the presence of emphysema on CT scan independently of the degree of airway obstruction or smoking history [6,7]. These findings might implicate a pathophysiological link between COPD and lung cancer beyond that of smoking [8].

COPD, however, is a heterogeneous disease where the different phenotypes may overlap, and it is unclear whether COPD patients with predominant airway inflammation have a similar increased lung cancer risk. Earlier studies have found an association between systemic inflammation and both frequent exacerbations and a higher mortality in COPD patients [9]. Nevertheless, a potential link between systemic inflammation and lung cancer development has not been sufficiently explored. Research on this topic may be useful both for finding cancer biomarkers for detection of early cancer, as well as gaining a better understanding of mechanisms by which lung tissue in some COPD patients undergo malignant transformation.

Our study aimed to evaluate several different COPD phenotypes and characteristics as risk factors for the development of lung cancer, combining clinical data and systemic

inflammatory markers from a large COPD cohort study with longitudinal follow up, merged with data from the Norwegian cancer registry.

Materials and methods

Study population

433 subjects with COPD and 279 healthy controls, all between 40 and 76 years old, were recruited to the Bergen COPD Cohort Study between 2006 and 2009 [10]. Both COPD patients and controls had a smoking history of more than 10 pack-years. All COPD patients had a clinical diagnosis of COPD, a post-bronchodilation test with FEV_1/FVC-ratio < 0.7, and FEV_1 < 80 % of predicted value. Exclusion criteria were known cancer within 5 years prior to entry, asthma or lung diseases other than COPD, active inflammatory disorders, and COPD exacerbations 4 weeks prior of inclusion, this latter category could be included later. The Regional Committee for Medical and Health Research Ethics, region west approved the study (REK-Vest, case number 2014/2153). Informed written consent was obtained from all participants.

Data collection

All subjects were evaluated by a study physician at inclusion, including a clinical interview regarding respiratory symptoms, smoking history, comorbidities and medication use. Comorbidities were pooled to calculate Charlson Comorbidity Score (CCS). All patients performed spirometry, before and after bronchodilation with 0.4 mg salbutamol. COPD patients were categorized according to 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The diagnosis of lung cancer was obtained from the Norwegian Cancer Registry, where registration is mandatory by law, with near 100 % coverage among both healthy controls and patients (see also supplementary materials) [11]. Body composition was evaluated with bioelectrical impedance measurements. Cachexia was defined as a fat free

mass index (FFMI) less than 17 kg/m^2 or 14 kg/m^2 in men and women, respectively [12], which corresponds to the lower 95% confidence limit in a normal population [13]. Obesity was defined as a fat mass index (FMI) of more than 9.3 kg/m^2 in men or more than 13.5 kg/m^2 in women [13]. Emphysema was assessed by computer tomography (CT) of the lungs, defined as having more than 10% of emphysematous lung tissue, specified as tissue density of less than -950 HU. Chronic bronchitis was defined as having cough with phlegm for more than three months the year before inclusion.

Laboratory measurements

Peripheral blood sampling was performed as previously described [10]. The analysis of the 44 inflammatory markers was performed with enzyme immunoassays (EIAs) and magnetic bead multiplex assays (see supplementary files for details).

Statistical methods

The baseline comparison between the study populations (COPD patients vs controls, and cancer vs non-cancer subjects), was done using non-parametric tests (Wilcoxon rank-sum for continuous and χ^2-test for categorical variables).

A cox-regression model was fitted to evaluate risk factors of lung cancer in COPD patients vs smoking controls. Age, sex, smoking status, pack-years smoked, and body composition were adjustment factors. Similarly, for the evaluation of risk factors for lung cancer in COPD patients, a cox-regression model was fitted with adjustment using the same variables as described above. In addition, the COPD characteristics emphysema, chronic bronchitis, 2 or more exacerbations last year before inclusion, and the use of inhalation medication was added to the model one at a time, and kept in the model if the p-value was below 0.05.

The 44 biomarkers were to different degrees correlated, and for the statistical evaluation the markers were added one at a time to the model above. Due to multiple testing of biomarkers, a Bonferroni adjusted p-value below 0.05/45=0.0011 was demanded for statistical significance.

The combined analysis of the variety of systemic inflammation between subjects was performed using a principal component analysis (PCA). PCA is a data reduction method that extracts and transforms the variance from multiple inter-correlated biomarkers into a smaller number of independent variables/components[14]. Principal components with eigenvalues above 1 (average) were retained for analysis in the cox-regression model. The first four components, located above the breaking point of the scree-plot, all with eigenvalues above 2, were also visualized using scatterplots and correlation diagrams.

Results

The baseline characteristics of the study population are presented in Table 1. COPD patients were older, had different smoking habits and experienced cachexia and obesity more frequently than smokers without COPD. Thirty-one subjects had a diagnosis of lung cancer during follow up of which 28 where in the COPD group. The time between study inclusion and diagnosis of lung cancer varied between 48 days and 8.6 years.

Table 1 Baseline characteristics of the study population

Characteristics	Smoking controls (n=279)	COPD (n=433)	p-Value*
Age, mean (SD)	58.0 (10.0)	63.5 (6.9)	<0.01
Sex, No (%)			
Female	128 (45.9)	175 (40.4)	0.15
Male	151 (54.1)	258 (59.6)	
Smoking status, No (%)			
Ex	103 (36.9)	243 (56.1)	<0.01
Current	176 (63.1)	190 (43.9)	
Packyears, mean (SD)	32.1 (21.5)	40.4 (22.7)	<0.01
Body composition, No (%)			
Normal	248 (88.9)	242 (55.9)	<0.01
Cachectic	11 (3.9)	123 (28.4)	
Obese	20 (7.2)	68 (15.7)	

Charlson Comorbidity Score, No (%)			
0	197 (70.6)	0	<0.01
1	61 (21.9)	250 (57.7)	
2	16 (5.7)	102 (23.6)	
3	5 (1.8)	51 (11.8)	
4+	0	30 (6.9)	
Lung cancer, No (%)	3 (1.1)	28 (6.5)	<0.01

*χ^2 or Wilcoxon rank-sum test

Lung cancer histology

The different histology patterns are shown in Figure 1. Non-small cell lung carcinomas were dominant, with only one case of small-cell lung carcinoma.

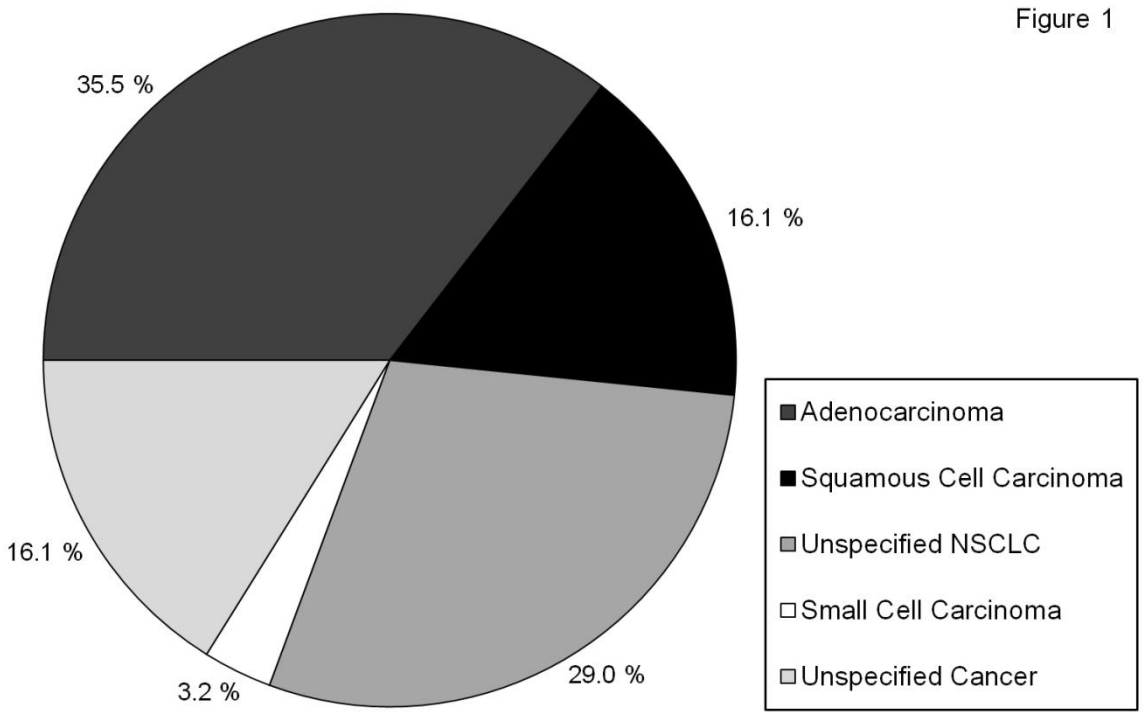

Figure 1
Distribution of lung cancer histology.

Comparison between COPD patients and controls

Table 2 shows unadjusted and adjusted hazard ratios in the combined COPD and control groups. COPD patients had a significantly higher risk of developing lung cancer during follow-up with a HR 5.0 (95% CI 1.5-17.1, p=0.01) after multivariable adjustment. Smoking status at inclusion or pack-years smoked were not associated with lung cancer.

Table 2. Risk factors for the development of lung cancer in COPD patients vs smoking controls, bi-and multivariable cox-regression

	Bivariable			Multivariable		
Variables	**HR**	**95 % CI**	**p-value**	**HR**	**95 % CI**	**p-value**
Age per 10 year increase	1.97	(1.24 to 3.13)	0.004	1.82	(1.04 to 3.20)	0.04
Sex						
Female	1			1		
Male	1.08	(0.53 to 2.20)	0.84	0.86	(0.41 to 1.82)	0.69
Smoking status						
Ex	1			1		
Current	0.57	(0.28 to 1.18)	0.13	1.18	(0.55 to 2.57)	0.67
Packyears per 10 units increase	1.12	(0.99 to 1.25)	0.06	1.03	(0.90 to 1.18)	0.68
*Body composition**						
Normal	1			1		
Cachectic	0.92	(0.31 to 2.72)	0.88	0.48	(0.15 to 1.48)	0.20
Obese	2.91	(1.31 to 6.48)	0.009	2.13	0.92 to 4.92)	0.08
*Patient category**						
Control	1			1		
COPD-patient	6.33	(1.92 to 20.8)	0.002	4.98	(1.45 to 17.1)	0.01

*All controls and patients were current or former smokers

Lung cancer risk related to COPD characteristics

Figure 2 shows the accumulated risk for developing lung cancer in COPD patients with and without CT-defined emphysema.

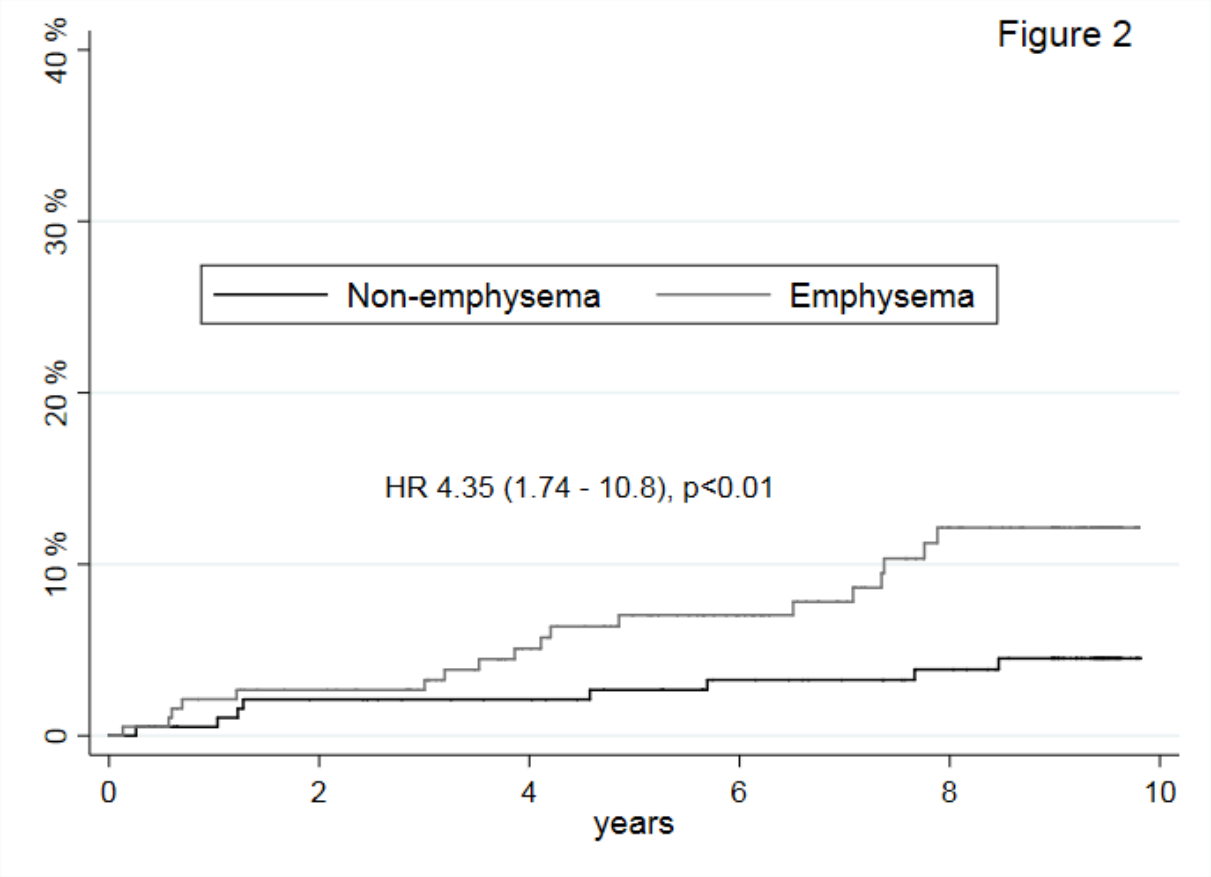

Figure 2
Incidence of lung cancer in patients with and without emphysema during follow up.

Table 3 shows the hazard ratios of the association of different COPD characteristics with lung cancer development. Factors associated with a higher lung cancer risk after multivariable adjustments were the presence of emphysema and/or obesity, whereas the use of inhaled corticosteroids (ICS) was associated with a lower risk (Table 3). Use of tiotropium was associated with a higher risk of lung cancer in the unadjusted model, but not after multivariable adjustment. When stratifying on gender, obesity only indicated a higher risk in males (HR 4.76; 1.4-16.0, p=0.01), but not in females (HR 1.34; 0.2-8.0, p=0.75). Similarly, the use of ICS indicated a lower risk in patients without emphysema (HR 0.13; 0.02-0.79, p=0.03), than in patients where emphysema was present (HR 0.47; 0.15-1.50, p=0.20).

Table 3. Risk factors for the development of lung cancer in COPD patients, bi-and multivariable cox-regression

	Bivariable			Multivariable	
Variables	HR	95 % CI	p-value	HR	95 % CI
Age per 10 year increase	1.76	(0.98 to 3.16)	0.06	1.77	(0.88 to 3.55)
Sex					
Female	1			1	
Male	0.93	(0.44 to 1.97)	0.86	0.61	(0.27 to 1.39)
Smoking status					
Ex	1			1	
Current	0.69	(0.32 to 1.49)	0.33	1.41	(0.57 to 3.48)
Packyears per 10 units increase	1.05	(0.92 to 1.21)	0.45	0.99	(0.85 to 1.17)
Body composition					
Normal	1			1	
Cachectic	0.58	(0.19 to 1.72)	0.32	0.32	(0.09 to 1.18)
Obese	1.99	0.85 to 4.66)	0.11	3.25	(1.25 to 8.45)
Emphysema					
No	1			1	
Yes	2.74	(1.19 to 6.31)	0.02	4.35	(1.74 to 10.8)
Use of inhaled steroids					
No	1			1	
Yes	0.74	(0.35 to 1.58)	0.44	0.40	(0.17 to 0.93)
GOLD-status (2007)*					
II	1				
III	1.08	(0.50 to 2.34)	0.84		
IV	0.78	(0.18 to 3.46)	0.75		
*Use of tiotropium**					
No	1				
Yes	2.20	(1.05 to 4.63)	0.04		
*Use of long-acting β2-agonists**					
No	1				
Yes	0.78	(0.40 to 1.97)	0.78		
*Exacerbations 12 months before inclusion**					
0-1	1				
2+	0.62	(0.19 to 2.05)	0.43		
*Chronic bronchitis**					
No	1				
Yes	1.21	(0.58 to 2.54)	0.61		
Charlson Comorbidity Score*					
1	1				
2	0.83	(0.30 to 2.27)	0.71		
3	2.29	(0.89 to 5.91)	0.09		
4+	1.44	(0.33 to 6.33)			

*p>0.05 in multivariable analysis

Biomarkers related to the development of lung cancer

Table 4a shows non-parametric analysis of 44 systemic biomarkers measured at study inclusion. Of the 44 markers, interleukin-6 (IL-6; p=0.01) and interferon gamma-induced

protein 10 (IP-10; p=0.02) were significantly associated with later development of lung cancer.

Table 4a Non-parametric analysis of biomarkers in non-cancer vs cancer in COPD-patients

	Mean values		
Biomarker[#]	**non-cancer**	**lung cancer**	**p-value***
Hemoglobin	14.53	14.19	0.12
Leucocytes	8.13	7.63	0.42
Granulocytes	5.57	5.12	0.46
Eosinophils	2.54	2.57	0.95
Platelet count	293.89	279.48	0.30
Activin-A	0.32	0.33	0.37
ALCAM	73.94	71.87	0.67
Basic FGF	63.91	60.48	0.34
CD-163	315.46	293.59	0.75
CRP	8.50	5.08	0.22
s-Creatinine	67.84	67.36	0.69
CXCL-16	783.28	836.98	0.31
Eotaxin	92.33	87.10	0.17
s-Ferritin	136.29	143.07	0.65
G-CSF	216.23	217.29	0.18
GDF-15	0.98	0.92	0.52
GM-CSF	98.45	56.44	0.39
IFN-γ	330.46	271.55	0.31
IL-1	0.96	0.55	0.59
IL-2	39.41	12.73	0.60
IL-4	15.06	15.86	0.39
IL-5	13.12	12.43	0.97
IL-6	2.96	1.13	0.01
IL-7	30.60	31.92	0.47
IL-8	33.65	35.35	0.39
IL-9	38.32	34.29	0.37
IL-10	80.53	45.93	0.87
IL-12	259.89	77.80	0.82
IL-13	163.04	43.66	0.48
IL-17	93.26	96.41	0.37
IP-10	768.84	1057.31	0.02
MBL	828.55	525.29	0.10
MCP-1	63.57	59.30	0.85
MCP-4	90.59	85.02	0.62
MIF	24.79	21.41	0.50
MIP-1α	8.83	8.17	0.83
MIP-1β	53.88	52.87	0.90
NAP-2	170.89	165.91	0.41
NGAL	75.69	68.55	0.30
OPG	5770.63	6247.31	0.29
PDGF-BB	1128.54	1093.75	0.81
TNF-R1	736.45	752.24	0.78
TNF-α	1.80	1.68	0.59
VEGF	48.20	46.19	0.66

Evaluation of biomarkers one at a time in the adjusted cox-regression analysis (Table 4b) showed that only IP-10 is significantly associated with lung cancer (HR 1.80; 1.32-2.45, p<0.001, per 1 SD increase), after multivariate adjustment. Higher levels of IP10 indicated a higher cancer risk in patients with emphysema (HR 2.05; 1.45-2.90, p<0.01), than in non-emphysema patients (HR 0.95; 0.38-2.40, p=0.92).

Table 4b Multivariate cox-regression of biomarkers and principal components in non-cancer vs cancer in COPD-patients

Biomarker	HR *	95 % CI	p-value[#]
Hemoglobin	0.78	(0.52-1.17)	0.23
Leucocytes	0.80	(0.51-1.25)	0.33
Granulocytes	0.77	(0.49-1.22)	0.27
Eosinophils	0.89	(0.55-1.43)	0.64
Platelet count	0.88	(0.56-1.38)	0.58
Activin-A	0.87	(0.57-1.35)	0.54
ALCAM	0.73	(0.41-1.33)	0.31
Basic FGF	1.04	(0.70-1.54)	0.84
CD-163	0.82	(0.46-1.44)	0.48
CRP	0.66	(0.35-1.24)	0.20
s-Creatinine	0.88	(0.56-1.38)	0.58
CXCL-16	1.24	(0.81-1.89)	0.32
Eotaxin	1.01	(0.65-1.57)	0.96
s-Ferritin	1.09	(0.81-1.46)	0.58
G-CSF	0.98	(0.62-1.55)	0.94
GDF-15	0.99	(0.59-1.65)	0.98
GM-CSF	0.56	(0.13-2.34)	0.43
IFN-γ	0.89	(0.45-1.76)	0.74
IL-1	0.60	(0.29-1.24)	0.17
IL-2	0.72	(0.12-4.24)	0.71
IL-4	1.09	(0.76-1.57)	0.64
IL-5	1.03	(0.70-1.52)	0.89
IL-6	0.25	(0.02-3.61)	0.31
IL-7	1.08	(0.82-1.43)	0.59
IL-8	1.16	(0.80-1.68)	0.44
IL-9	0.93	(0.57-1.51)	0.77
IL-10	0.91	(0.50-1.66)	0.76
IL-12	0.16	(0.00-75.8)	0.56
IL-13	0.46	(0.07-3.06)	0.42
IL-17	1.05	(0.71-1.57)	0.80
IP-10	1.80	(1.32-2.45)	<0.001
MBL	0.68	(0.38-1.23)	0.20
MCP-1	0.97	(0.64-1.46)	0.87
MCP-4	0.82	(0.82-1.28)	0.37
MIF	0.78	(0.46-1.32)	0.35
MIP-1α	0.99	(0.48-2.02)	0.98
MIP-1β	0.92	(0.60-1.40)	0.68
NAP-2	0.87	(0.61-1.26)	0.47
NGAL	0.70	(0.47-1.11)	0.13
OPG	1.07	(0.72-1.60)	0.74
PDGF-BB	0.96	(0.63-1.48)	0.87

TNF-R1	0.92	(0.61-1.38)	0.69
TNF-α	1.04	(0.68-1.58)	0.84
VEGF	1.00	(0.67-1.51)	0.97
Principal components	**HR**	**95 % CI**	**p-value**
PC1	1.00	(0.89-1.14)	0.94
PC2	0.96	(0.78-1.18)	0.69
PC3	0.87	(0.66-1.15)	0.34
PC4	0.74	(0.54-1.01)	0.06
PC5	1.26	(0.90-1.76)	0.17
PC6	0.71	(0.50-1.00)	0.05
PC7	0.89	(0.60-1.31)	0.54
PC8	1.04	(0.69-1.56)	0.85
PC9	1.17	(0.79-1.73)	0.44
PC10	0.83	(0.52-1.32)	0.43
PC11	0.59	(0.38-0.92)	0.02

* per 1 SD increase

The combined effect of the 44 biomarkers was evaluated by principal component analysis using components 1-11 with eigenvalues above 1, representing 71% of the cumulative variance of the biomarkers. The values of the different eigenvectors, and the markers included in each principal component, are shown in the supplementary material. The principal components 1-11 were also analysed using the cox-regression model described above, but no significant statistical difference was observed between lung cancer and non-cancer patients (Table 4b). The distribution of component 1-4 of the principal component analysis of the 44 biomarkers in lung cancer vs non-cancer patients is shown in Figure 3.

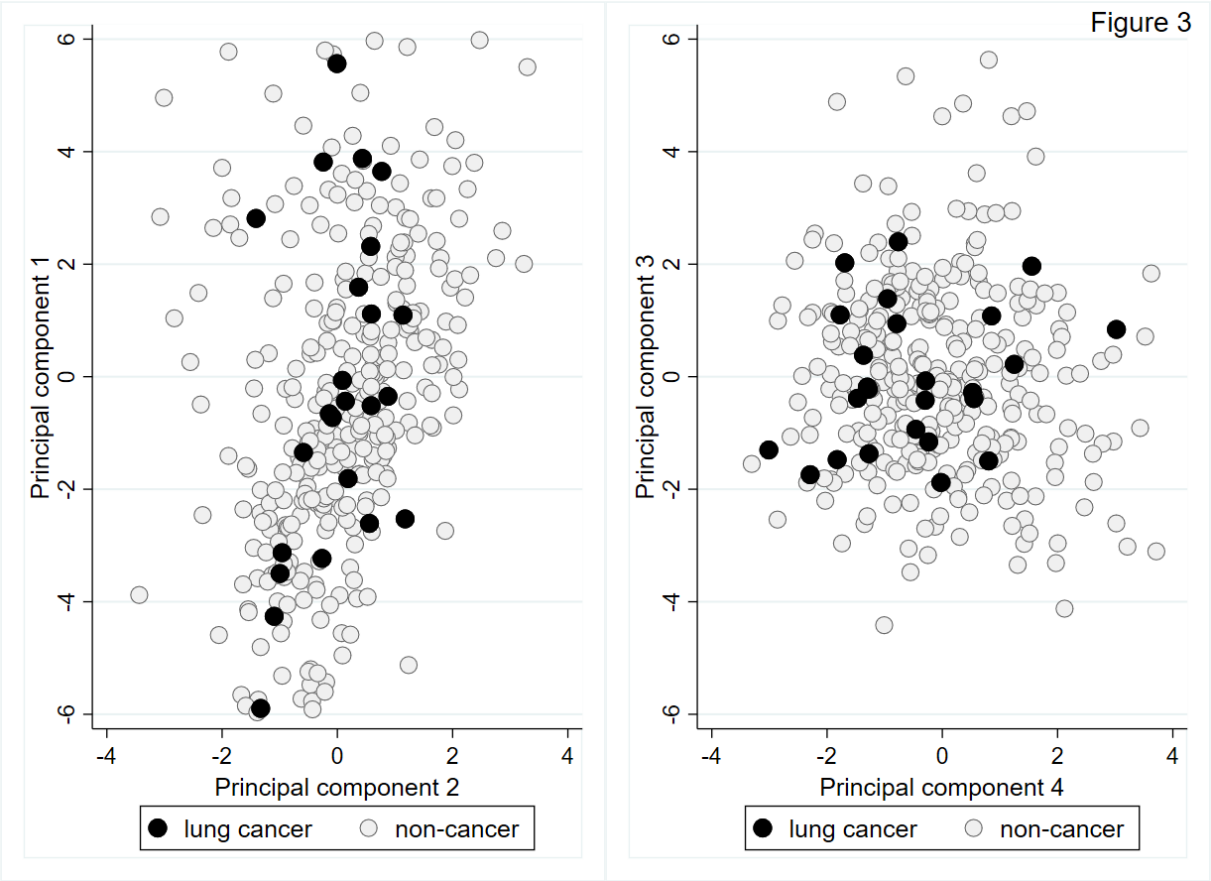

Figure 3
Systemic inflammation in non-cancer vs lung cancer patients represented by principal components 1-4 of the systemic inflammatory markers, measured at study inclusion. Scatterplots of components 1 vs 2 and 3vs 4 shows no visually nor statistically significant difference between the groups.

Figure 4 shows the correlations between the different COPD characteristics and biomarkers of systemic inflammation represented by the principal components 1-4. There was a higher degree of correlation between the components and the COPD characteristics of frequent exacerbations and chronic bronchitis, than with lung cancer or emphysema.

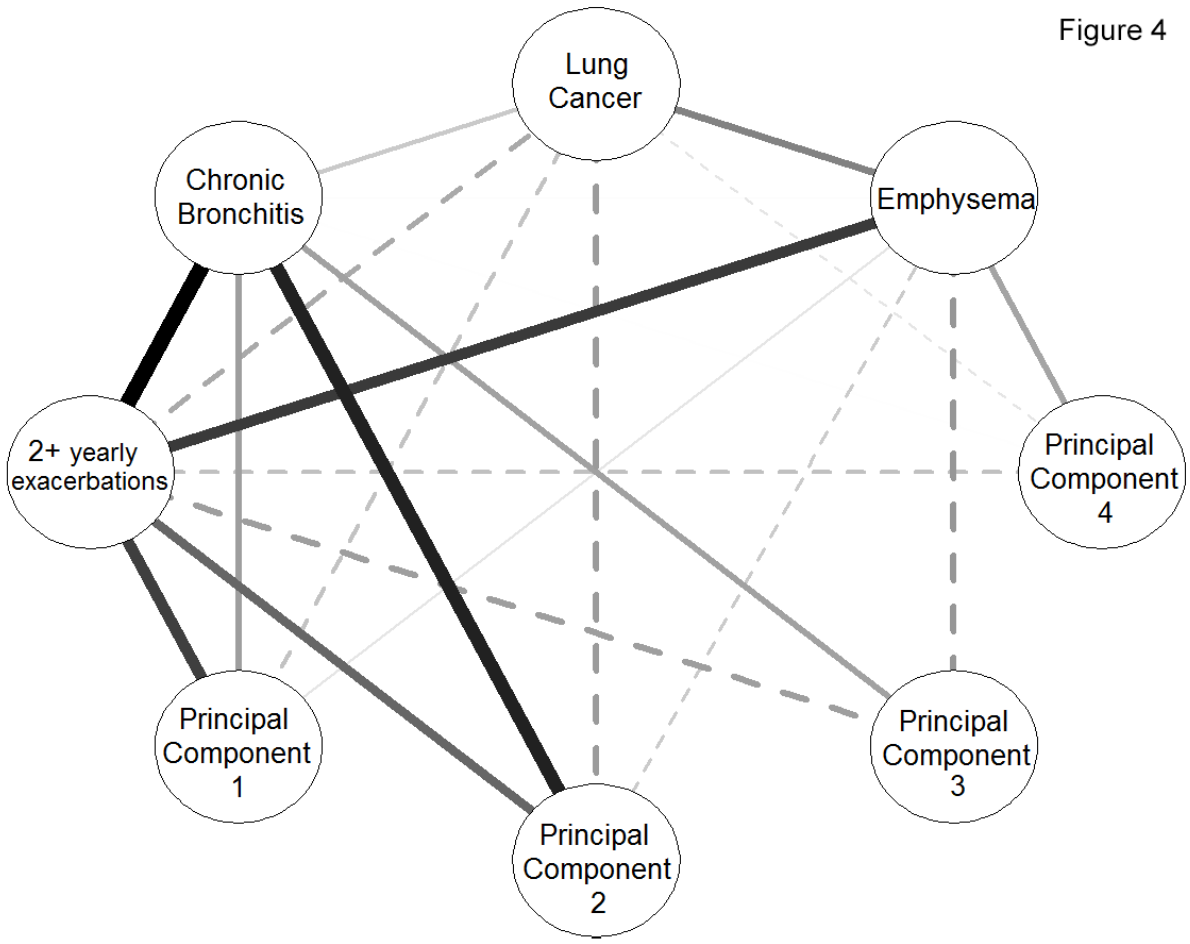

Figure 4
Correlation diagram showing the relations between COPD characteristics and systemic inflammation at study inclusion represented by principal components 1-4. Thicker line indicates larger degree of correlation, solid line indicates positive correlation, dashed line indicates negative correlation.

Discussion

The results of this study showed that both current and ex-smoking COPD patients, irrespective of packyears smoked, had an increased risk of lung cancer. Further, the presence of emphysema and obesity was associated with an increased lung cancer risk, whereas the use of ICS was associated with a reduced risk. Among 44 systemic biomarkers, only IP-10 was significantly associated with the development of lung cancer after multivariable adjustment.

The study did not demonstrate any clear association between lung cancer and the COPD characteristics of chronic bronchitis, frequent exacerbations, or markers of systemic inflammation beside IP-10.

A diagnosis of COPD, and especially with the presence of emphysema, was a risk factor for developing lung cancer in our study. Current smoking or a high pack-year count did not increase the risk, suggesting the persistence of lung damage even after quitting smoking, or after a moderate amount of smoking. These findings are in accordance with earlier studies which have demonstrated a relationship between a diagnosis of COPD and lung cancer or death of lung cancer irrespective of the amount of smoking [3-5,15]. Subsequent studies have further evaluated this relationship, where the presence of emphysema in COPD patients was associated with both a diagnosis of lung cancer, but also death due to lung cancer as well as non-pulmonary cancer [6,7,16]. The co-existence of emphysema and lung cancer may obviously be ascribed to their common risk factor of noxious airway exposure. However, a common pathophysiology of these two conditions is nevertheless more difficult to explain, with apoptosis and protein degrading as main characteristics of emphysema as opposed to the excessive cell growth in cancer. Possible mechanistic explanations of cancer development include accelerated proliferation of epithelial cells resistant to apoptosis, dysfunction of proteinase-regulation, and increased generation of pro-inflammatory cells, cytokines and reactive oxygen species [8,17].

There is extensive research data linking systemic inflammation and cancer in general [18]. In lung cancer, this relationship is less well described, but several studies have demonstrated elevated inflammatory mediators in patients with established lung cancer [19-22]. An important study question to address was whether indices of systemic inflammation could predict lung cancer in COPD patients. Interrelated phenotypic attributes such as chronic bronchitis and frequent exacerbations were also associated with increased systemic inflammation, but none

of them had a significant association with the development of lung cancer. We evaluated inflammatory biomarkers both individually as well as combined with principal component analysis, with mostly negative findings regarding any predictive value of lung cancer. However, the principal component analysis indicated a closer association between inflammatory markers and patients with mainly chronic bronchitis and exacerbations, rather than in patients with emphysema or with high lung cancer risk, suggesting the existence of different pathophysiological/immunological pathways underlying the different COPD phenotypes.

Among 44 serum/plasma biomarkers, only high levels of IP-10 were associated with increased lung cancer risk. IP-10 (CXCL-10) is induced by IFNγ, and is frequently used as a marker of viral infection [23,24]. Its functions include induction of chemotaxis, regulation of cell growth/apoptosis and angiogenesis. Spaks et al found elevated serum IP-10 in lung cancer patients [25], and high expression is also seen in other cancer types. The role of IP-10 in cancer may depend on its receptor; it may be involved in tumor growth inhibition through angiostatic or immunogenic actions or in direct tumor growth stimulation. The role of IP-10 in either COPD or lung cancer is yet unclear, and thus it should be further investigated.

The association between the use of ICS and a lower risk of lung cancer is in accordance with prior observational studies [26-28], and may indicate a protective effect of ICS. The above mentioned link between inflammation and cancer may be modified by ICS, and the potential protective mechanisms of ICS may include reduced secretion of carcinogenic cytokines or growth-factors in the lungs, as well as inhibition of proto-oncogene expression [29,30]. On the other hand, a similar effect has not been found in randomized controlled studies [31,32], and the observed effect of ICS may be due to a protopathic bias. However randomized controlled trials are neither designed nor have had a sufficient follow up time to evaluate lung cancer risk, thus a potential preventive effect of ICS is still possible although unproven [33,34].

A major finding in the present study was an independent association between obesity and lung cancer development in COPD patients, primarily reflecting an association in males. Obesity is described as a risk factor of several variants of cancer [35], however, regarding lung cancer, several prior studies report opposing findings where some have reported a protective effect of high BMI [36,37]. This is, nevertheless, a complex matter to study, where several confounding factors such as smoking habits, genetics and dietary issues may affect the findings in the different study populations [38,39]. Recently, a large study where 23,732 incident lung cancer cases were identified suggested that central obesity, particularly concurrent with low BMI, could help identify high-risk populations for lung cancer [40], and future studies in COPD patients in relation to cancer development should also include fat distribution as a parameter.

There is an ongoing international debate on lung cancer screening [41]. Early detection of lung cancer using low-dose computer tomography is probably the most important measure in reducing mortality [42]. Most screening protocols consider smoking and aging as the most important risk factors, though some recent studies promotes the inclusion of additional parameters to narrow the screening population [43-45]. Screening appears to be more advantageous in case of emphysema phenotype of COPD, but less in case of COPD with chronic bronchitis or other forms of chronic inflammation. The results of our study support narrowing the screening population based on presence of airflow limitation as well as indications of emphysema.

The strengths of our study were its prospective design with outcomes from a mandatory national registry, and the availability of detailed information on a large number of patients allowing adjustment of multiple variables.

Some limitations should be mentioned. First, the patients were not randomized, and therefore data interpretation regarding causality is difficult. Second, the serum/plasma inflammatory

markers were measured only at entry, and thus it is uncertain to what extent this is representative of lung inflammation or whether the degree of systemic inflammation in the subjects is altered during follow-up. Third, the study population represents an outpatient clinic population, with exclusion of GOLD class 1 patients and, thus the results may not be applicable to a COPD population with early stage disease. Finally, there was no systematic screening of lung cancer. Thus, although the Norwegian Cancer Registry has a high degree of completeness, we cannot exclude cases of non-reported lung cancer among patients or controls.

The present study clearly underscores the necessity of looking at COPD as a heterogeneous disease, where the different phenotypes not only require different diagnostics and treatment, but where they also incorporate different risks of adverse events such as lung cancer development. The idea of using serum/plasma biomarkers in early lung cancer screening may presently seem challenging, but an increasingly easier access to large multiplex bioassays and a better understanding of the pathophysiologic mechanisms behind the COPD phenotypes might change this view in the near future.

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Author contributions:
GRH, JAH, PSB and TMLE designed the study. GRH, RG, JAH, PSB, LL, JG, CAG, EG and TMLE obtained the data. GRH and TMLE analysed the data and drafted the manuscript, and are the guarantors of the paper. All authors have seen and approved the final version of the manuscript.

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