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Acute exacerbations of COPD and risk of lung cancer in COPD patients with and without a history of asthma

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ABSTRACT

Rationale: There is limited knowledge on the effect of acute exacerbations in chronic obstructive pulmonary disease (AECOPD) on lung cancer risk in COPD patients with and without a history of asthma. This study aims to examine whether AECOPD is associated with risk of lung cancer, and whether the effect depends on a history of asthma.

Methods: In the GenKOLS study of 2003–2005, 852 subjects with COPD performed spirometry, and filled out questionnaires on smoking habits, symptoms and disease history. These data were linked to lung cancer data from the Cancer Registry of Norway through 2013. AECOPD, measured at baseline was the main predictor. To quantify differences in lung cancer risk, we performed Cox-proportional hazards regression. We adjusted for sex, age, smoking variables, body mass index, and lung function.

Measurements and results: During follow-up, 8.8% of the subjects with, and 5.9% of the subjects without exacerbations were diagnosed with lung cancer. Cox regression showed a significant increased risk of lung cancer with one or more exacerbations in COPD patients without a history of asthma, HRR = 2.77 (95% CI 1.39–5.52). We found a significant interaction between a history of asthma and AECOPD on lung cancer.

Conclusions: AECOPD is associated with an increased risk of lung cancer in COPD patients without a history of asthma.

Introduction

Compared to healthy smokers, smokers suffering from COPD have an increased risk of lung cancer [1]. Emphysema [2] and airway obstruction [1] increase the risk of lung cancer, but there is limited knowledge on how other features of COPD, such as acute exacerbations in COPD (AECOPD) affect lung cancer incidence.

Chronic inflammation is central to the development of COPD [3]. Inflammation is further thought to play an essential part in the pathogenesis of lung cancer in COPD patients [4]. Since both local and systemic chronic inflammation is a characteristic of COPD exacerbations [5–7], one might hypothesize that acute exacerbations in COPD increase the risk of lung cancer.

Few studies have examined AECOPD and the risk for lung cancer, and these studies show conflicting results [7,8]. In a nested case–control study from the COPDGene cohort, patients with COPD with incident lung cancer reported a higher frequency of exacerbations 12 months prior to study enrolment [8]. In another study, including 433 COPD patients and 279 healthy controls, AECOPD was not related to the increased incidence of lung cancer during 9 years of follow-up [7].

Patients with a history of asthma have often been excluded from COPD studies. This was also the case with the study of Husebø et al. [7]. COPD patients with a history of asthma may have a different exacerbation phenotype compared to COPD patients without a history of asthma [9]. Hence, the risk of lung cancer from AECOPD might vary by a history of asthma [10].

We had access to a population-based cohort of subjects with COPD, which included information regarding asthma diagnosis as well as AECOPD the year before inclusion. This information was linked to data from the Cancer Registry of Norway [11] in order to 1) explore whether AECOPD was associated with an increased risk of lung cancer during 10-year follow-

up, and 2) whether the risk of lung cancer due to AECOPD differed based on a history of asthma.

Materials and methods

Prior to enrolment, information was given and written informed consent obtained from all study subjects. The study was reviewed and approved by the Western Norway Regional Committee for Medical and Health Research Ethics, reference number 2010/2575/REK vest.

Study population

The subjects in the current analyses were all participants in the GenKOLS study (Genetic COPD study) conducted between January 2003 and January 2005 in Bergen, Norway. Details on the GenKOLS population are presented elsewhere [12]. GenKOLS was a case–control study, and the subjects in the current analyses comprised the COPD cases only. Participants were 40–85 years of age and had a smoking history of at least 2.5 pack-years at baseline. COPD was diagnosed when post-bronchodilator FEV1/FVC was <0.70 and FEV1 < 80% predicted. Baseline examinations included a detailed questionnaire on smoking habits, respiratory symptoms, and disease history, as well as pulmonary function tests. We also obtained incidence data from the Cancer Registry of Norway [11] throughout the year 2013. All subjects with a cancer diagnosis before inclusion were excluded from the analyses. Due to missing information on emigration date, also four individuals that emigrated during follow-up were excluded.

Main variables

Lung cancer incidence was the primary outcome variable. We retrieved information on the study participants who developed lung cancer from January 2003 through December 2013 from the Cancer Registry of Norway, which contains data on all individuals in Norway diagnosed with cancer [11]. Registration is regulated by law, and registration of patients is mandatory both for pathologists and clinical doctors, with a near 100% completeness [13]. Lung cancer was identified in the registry by the ICD-10-code C34. The data from the Cancer Registry included time of diagnosis and histologic classification of the cancer.

Acute exacerbations of COPD (AECOPD) was the main predictor of interest. AECOPD was defined as events where courses of antibiotics were administered due to lung disease in the last 12 months preceding inclusion. The question asked was, 'Have you had treatment with antibiotics for lung disease during the last 12 months?' and "If YES, how many times?

Participants were considered to have a history of asthma if they gave affirmative answers to both: 'Have you had asthma?' and 'if yes, was this confirmed by a doctor?'

Other variables

Smoking status was defined as the current status at inclusion. Pack-years of tobacco smoking was defined as (number of cigarettes smoked per day/20) x number of years smoked. We also recorded age at onset of smoking. Educational level, height, weight, and pulmonary function tests were measured at inclusion [14]. Spirometries were performed according to the American Thoracic Society standards [15]. Local reference values for FEV1 and FVC were used [16]. The date of death was obtained by linkage to the Norwegian National Cause of Death Registry [17]. Patients were followed until a diagnosis with lung cancer, date of death, or end of follow-up in December 2013, whichever came first.

Statistical analyses

Since only eight individuals developed lung cancer in the group with two or more exacerbations in the preceding year, AECOPD was analysed as a dichotomous variable (0 vs. 1 or more exacerbations). The Kaplan-Meier method was used to calculate and plot probabilities for developing lung cancer. To quantify differences in the risk of developing lung cancer, we performed Cox-proportional hazards regression and reported hazard rate ratios (HRR) [18]. Covariates in the adjusted analyses were sex, age, pack-years, age of onset of smoking, smoking status at inclusion, body mass index (BMI), and FEV1. The interaction between AECOPD and a history of asthma on lung cancer was also tested.

Furthermore, analyses stratified by a history of asthma were presented. To take mortality into account, as a competing risk, we also performed Fine and Gray competing risk analyses for the probability of developing cancer. The results from the Fine and Gray model [19], presented as sub-hazard rate ratios (SHRR), are presented in the online supplement.

All analyses were performed using STATA version 16. (StataCorp. TX, USA). A two-sided significance level of 0.05 was applied for all analyses.

Results

Altogether, there were 852 COPD patients included in the study, of which 38.4% were women. The mean age was 65.1 (SD = 10.1) years, 30.5% had one or more

exacerbation during the last 12 months before inclusion, and 49.5% reported a history of asthma at inclusion. COPD patients with a history of asthma comprised more women, had a lower smoking consumption in terms of pack-years, had more exacerbations 12 months prior to inclusion, and a lower lung function in terms of FEV1 in percent predicted than COPD patients without a history of asthma (Table 1).

For the entire sample, 8.8% of the COPD patients with and 5.9% of the COPD patients without exacerbations were diagnosed with lung cancer. Average time from inclusion to lung cancer diagnosis was 4.5 years (range: 43 days to 10.4 years), and did not differ significantly between those with and without exacerbations. For the COPD patients without a history of asthma, and at least one exacerbation 12 months before inclusion 14 individuals, 14.0%, got a lung cancer diagnosis, whereas 9 individuals, 5.6%, got lung cancer in the group of patients with a history of asthma, and at least one exacerbation 12 months prior to inclusion.

In unadjusted Cox-regression analyses on the entire sample, increasing age and decreasing BMI were significantly associated with the risk of lung cancer, the HRR being 1.03 (95% CI 1.00–1.06) per year, and HRR = 0.93 (95% CI 0.88–0.99) per kg/m2, respectively. Exacerbation status at inclusion was also related to the risk of lung cancer (borderline non-significant). The HRR for lung cancer in those with one or more exacerbations as compared to no exacerbations 12 months before inclusion was 1.58 (95% CI 0.93–2.67).

In COPD patients without a history of asthma, those with one or more exacerbations had a higher probability of lung cancer than those without exacerbations (Figure 1(a)), while for COPD patients with a history of asthma, the probability of lung cancer did not differ between those with and without exacerbations (Figure 1(b)).

For COPD patients without a history of asthma, we found that those with exacerbations had an HRR for lung cancer of 2.77 (95% CI 1.39–5.52) compared to those without exacerbations. For COPD patients with a history of asthma, the corresponding number was 0.90 (95% CI 0.40–2.05) (Table 2). When adjusting for sex, age, smoking status and consumption, FEV1, and BMI at inclusion, the risk ratio for lung cancer in those with exacerbations (compared to those without) remained significantly increased in the non-asthma group and was still insignificant in those with a history of asthma (Figure 2).

Adding an interaction term between a history of asthma and exacerbation status in the adjusted Cox-regression analysis on the entire sample, we found that the interaction term reached a level of significance. This shows that there is an additional effect of exacerbations for patients without a history of asthma (Table E1, online supplement).

Table 1. Baseline characteristics by a history of asthma.

	No asthma	Asthma	P-value
Subjects, n	430	422	
Sex, female (%)	30.5	46.5	<0.001
Years of age, mean (SD)	64.9 (10.2)	65.4 (10.0)	0.528
Current smokers (%)	47.0	45.3	0.615
Pack years, median (25/ 75 percentile)	31.0 (21/ 44)	25.9 (18/ 39)	<0.001
Age of onset of smoking, mean (SD)	18.4 (4.5)	18.9 (5.8)	0.098
~AECOPD, mean (SD)	0.3 (0.8)	0.8 (1.5)	<0.001
Lung cancer (%)	7.7	5.9	0.311
§BMI (kg/m^2), mean (SD)	25.3 (4.8)	25.7 (5.2)	0.304
Education (%)			0.002
Primary	26.4	35.8	
Secondary	59.6	55.8	
University	14.0	8.4	
^PB FEV1 pp, mean (SD)	54.6 (17.3)	47.0 (17.0)	<0.001

~ Acute exacerbations in COPD, §Body mass index, ^Post-bronchodilator FEV1% predicted.
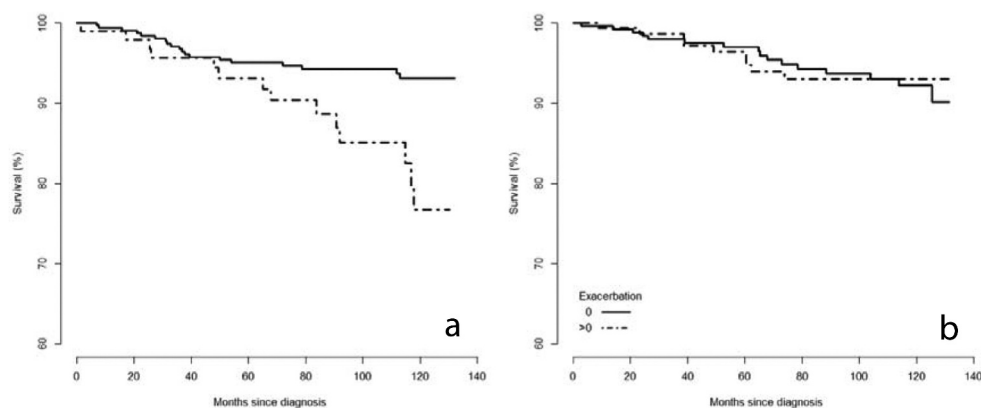

Figure 1. Free of cancer estimates for lung cancer by AECOPD in COPD patients without (a) and with a history asthma (b).

Table 2. Unadjusted Cox-regression analyses. The risk for lung cancer in COPD patients with and without a history of asthma.

	No asthma		Asthma	
	'HRR	95% CI	'HRR	95% CI
Sex	1.72	0.75–3.97	0.83	0.38–1.82
Age	1.03	0.99–1.07	1.02	0.98–1.07
Pack Years	1.01	0.99–1.03	1.01	0.99–1.03
Current smokers	0.71	0.35–1.41	0.84	0.38–1.86
Age of onset of smoking	0.96	0.88–1.05	1.02	0.95–1.08
^PB FEV1 pp	0.83	0.69–1.01	0.91	0.72–1.16
§BMI (kg/m^2)	0.91*	0.84–0.98	0.96	0.88–1.04
Education	0.70	0.40–1.23	0.62	0.31–1.21
~AECOPD, 1 or more	2.77**	1.39–5.52	0.90	0.40–2.05

'Hazard Rate Ratio, ^Post-bronchodilator FEV1% predicted, divided by 10. §Body mass index, ~Acute exacerbations in COPD, * $p < 0.05$, ** $p < 0.01$.

The Fine and Gray competing risk model for the probability of developing lung cancer, taking patient mortality into account, gave virtually the same results as the Cox-regression analysis. Results are presented in the online supplement (Table E2).

The histological subtypes of lung cancer comprised 33.9% adenocarcinoma, 22.0% squamous cell, 10.2% small cell lung cancer, 25.4% unspecified non-small cell lung cancer, and 8.5% had unknown histology type. No relationship between AECOPD and histological subtypes was found (data not shown).

Discussion

The main finding of this study on subjects with COPD followed for 10 years was that AECOPD was only significantly associated with an increased risk of lung cancer in COPD patients without a history of asthma. The association was independent of sex, age, BMI, lung function, pack-years, age of onset of smoking, and smoking status at baseline.

Our findings are in line with Carr et al. in showing an association between AECOPD and lung cancer risk [8]. In the study by Carr et al., they saw an effect on lung cancer incidence already after 1 year of follow-up, whereas we saw it after 5 years (Figure 1). A potential explanation for this difference is that Carr et al. followed a cohort of subjects with and without COPD, whereas we had COPD patients only. They also had a case–control study design comparing lung cancer cases to non-lung cancer cases. When exploring the association between AECOPD and lung cancer in COPD cases only, they were not able to produce significant results. They followed their cohort for an average of 5.7 years, of which 24% had <5 years follow-up, and 10% of their subjects had no follow-up. Hence, they expected some lung cancers to be unreported and did not know their survival outcomes [8]. In the present study, we had 10 years of follow-up and access to the Cancer Registry of Norway with practically 100% coverage. Another study looking at several risk factors for lung cancer in COPD found no association between AECOPD and risk of lung cancer [7]. They detected 32 lung cancer cases and did
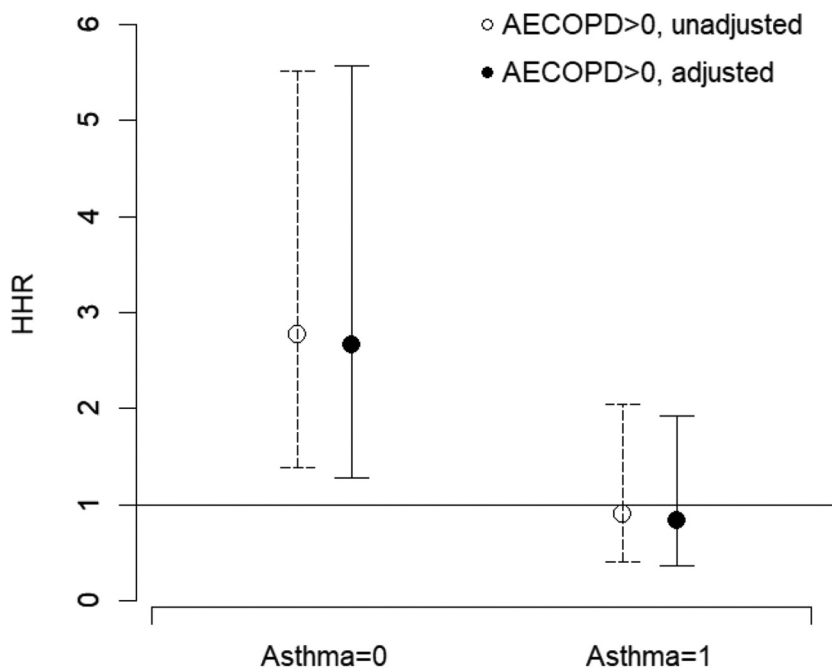
Figure 2. Unadjusted and adjusted Cox-regression analyses. Risk for lung cancer in COPD patients without and with a history of asthma.

Adjusted for sex, age, pack-years, age of onset of smoking, smoking status, BMI, and FEV1.

not report the number of exacerbations. The lack of an association in their study could be due to small numbers and low statistical power.

We observed a significant association between AECOPD and lung cancer risk only in COPD patients without a history of asthma. To our knowledge, this is the first study to explore whether there is a difference between the effect of AECOPD on lung cancer in COPD patients based on a history of asthma.

This finding could have several explanations. First, one recent retrospective study found that coexisting asthma in COPD patients was associated with decreased risk of lung cancer [10]. This could indicate that COPD patients with a history of asthma represent a phenotype caused by different mechanisms, and therefore, a reduced risk of lung cancer. Their study did, however, have several weaknesses. COPD was defined without spirometry, and they were not able to adjust for lung function in the statistical analyses. They also lacked information on tobacco exposure, which might explain lower lung cancer risk for those with asthma. Second, several studies have found a decreased risk of lung cancer with inhaled steroids [7,20–22]. This could be due to reduced airway inflammation, and that decreased cell turnover lowers the risk for the propagation of genetic errors [20]. Patients with a history of asthma might have used more inhaled steroids, and COPD patients with clinical features similar to asthma are found to respond better to corticosteroids than COPD patients without [23]. However, the same effect of ICS on lung cancer has not been seen in randomized controlled trials [24,25]. On the other hand, randomized controlled trials might not have sufficient follow-up time or the proper design to examine the effect on lung cancer risk by ICS. Hence, a possible protective effect of ICS on lung cancer might still be present, but unproven [26,27]. Third, inflammation is an essential part of the pathogenesis in lung cancer development in patients suffering from COPD [4]. COPD is considered a systemic disease [28] in which the frequent exacerbations phenotype is associated with increased systemic inflammation [7]. AECOPD have different triggers, clinical manifestations, biomarkers, comorbidities, and exacerbation frequencies [9]. Neutrophilic inflammation driven by CD8 + T-cells are often seen in COPD, whereas inflammation in asthma patients more often is eosinophilic and mediated by CD4 + T-cells [29]. One might hypothesize that the neutrophilic inflammation increases lung cancer risk more than the eosinophilic. Fourth, triggers such as viruses and bacteria are thought to cause most exacerbations [30,31]. Some bacteria and more

viruses play an essential part in cancer development of other types of cancer [32,33]. It could be that some bacteria or viruses lead to cancer development also in the lungs. We do not know whether different COPD phenotypes have different triggers to AECOPD. Fifth, tobacco exposure is a prevalent risk factor for both lung cancer and COPD. COPD patients with a history of asthma smoked less than COPD patients without a history of asthma (Table 1). It could be that the chronic inflammation and enzymatic imbalance caused by tobacco is less present in asthma patients. Also, other possible confounders should be considered. The group without a history of asthma had higher educational level than the group with a history of asthma, implying no beneficial effect on lung cancer risk from education (Table 1). We adjusted for pack-years, age of onset of smoking, smoking status, age, sex, and lung function in the adjusted analyses, but residual confounding cannot be ruled out.

For the statistical analyses in this article, we used Cox-proportional hazards regression. Using the increasingly popular Fine and Gray competing risk regression, taking patient mortality into account, we found virtually the same as using Cox-regressions (Table E2). Still, one could argue that competing risk models are better suited for studying the clinical prognosis of the patient since the risk for the patient dying is accounted for [18].

There are several strengths in this study. First, it is a sizeable single-centre study that allows for extensive adjustment for relevant confounders. Second, participants were not sampled from a cancer screening trial, but a community-based sample followed for more than 8000 person-years. Third, it is a prospective study in which all lung cancers were incident cases diagnosed after baseline measures of exacerbations. Fourth, cancer diagnosis was taken from the Cancer Registry of Norway, which has close to a 100% inclusion rate and provide histology verified diagnosis [13]. Fifth, spirometry was performed by all participants, and chronic airway obstruction verified in all subjects with COPD.

The present study also has some limitations. First, the GenKOLS study was initially designed as a case-control study to examine subjects with COPD. We, therefore, have few cancer cases compared to those sampled in screening trials. Due to small numbers of lung cancer, the lack of association between AECOPD and histological subgroups of lung cancer should be interpreted with care. Second, moderate to severe AECOPD is usually treated with either antibiotics, systemic steroids, or both, based on clinical manifestation.

In our study, we only had data on events that were treated with antibiotics. Therefore, we do not know if there were any events that needed steroid treatment. The numbers of exacerbations were, however, similar to the numbers presented by the comparable GeneCOPD study [8]. Furthermore, some of the events that had been treated with antibiotics could have been a pneumonia and not an exacerbation. Previous pneumonia is found to predict lung cancer [34] and cannot be ruled out as a potential source of bias. Third, the asthma diagnosis was questionnaire-based and presented a history of asthma as opposed to a current clinical diagnosis. It might be that some of the subjects received a wrong diagnosis earlier in life. The characteristics of COPD patients with a history of asthma were in line with another study in seeing a smaller amount of tobacco consumption, lower FEV1, and higher exacerbation frequency, compared to COPD patients without a history of asthma [35]. The prevalence of asthma in this population of subjects with COPD is in line with other epidemiological studies [36–39], but higher than in clinical trials [40,41]. A misclassification of asthma is likely to be non-differential when comparing those with and without cancer, due to a prospective study design where both participants and the study crew were unaware of the future lung cancer diagnosis at the time of inclusion. Fourth, never-smokers were not included in the study, which prevented us from generalizing the findings to a never-smoking population. We did, however, include tobacco consumption down to 2.5 pack-years. Fifth, we did not include GOLD stage I, which in some studies have shown to have the highest incidence of lung cancer [42]. Sixth, we used a fixed ratio for COPD diagnosis, which might lead to over-diagnosis in elderly subjects when compared to the lower limit of normal.

Clinical relevance

We know that COPD is a risk factor for lung cancer [43]. Nevertheless, most randomized control trials have had recruitment criteria based on age and smoking history alone [44–49]. This study suggests that AECOPD and asthmatic features of COPD should be considered when evaluating those at higher risk. More studies, including validated information on acute exacerbations in COPD patients with and without a history of asthma, are needed to better understand which mechanisms link COPD and lung cancer. As we learn more about the clinical phenotypes of COPD, one can easier target COPD patients at higher risk of lung cancer and determine who to include in screening trials.

Conclusion

Acute exacerbations of COPD are associated with an increased risk of lung cancer in those without a history of asthma, but not in those with a history of asthma.

Disclosure statement

No potential conflict of interest was reported by the authors.

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