Chronic obstructive pulmonary disease and risk of lung cancer

Ane Aamli Gagnat

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Scientific environment

The work presented in this thesis was performed in the period 2014-2020. It started as a part of the university program, Medical Student Research Program, or Forskerlinjen, which I attended as a parallel program to my medical studies from fall 2014 till spring 2019. I was a fulltime Ph.D. student from September 2019. The work emerged from the Bergen Respiratory Research Group, Department of Clinical Science, University of Bergen. The group was led by Einar Thorsen and then Tomas M.L. Eagan. This thesis is anchored in the project "GenKOLS study", which was led by professor Amund Gulsvik

The University of Bergen funded my Ph.D. position and three years of my position at the Medical Student Research Program (Forskerlinjen).

The supervisors during this work have been:

Per Bakke, professor, MD. Dean, Faculty of Medicine, University of Bergen

Miriam Gjerdevik, statistician, Ph.D. Department of Global Public Health and Primary Care, University of Bergen

Rune Nielsen, associate professor, MD. Department of Clinical Science, University of Bergen

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During my first year of medical school, I participated in a clinical study together with a friend, Maria. We had to drink e-coli and have our feces examined, isolated in the hospital for nearly one week. Amazingly enough, doing research seemed like a lot of fun. Especially, as opposed to memorizing chemical formulas, Latin and anatomical structures. Anne Berit Guttormsen was in charge of the clinical study, and I asked her for advice on which scientific environments to approach. She recommended neurology and the respiratory research group. I approached professor Gilhus in neurology who scared me off with a project within epidemiology. I did not want to spend my days in front of the computer with statistical software. Professor Bakke, however, promised data collection on real patients combined with data analysis, and even trips abroad to international congresses. His excitement made it impossible to reject the offer. First years later have I realized that Professor Bakke tricked me into working with epidemiology and statistical software in front of a computer. Yet, here I am, having had a rich time and having several people to thank for that.

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Abstract

Background: Lung cancer is a main cause of death in patients suffering from COPD and smokers with COPD have an increased risk of lung cancer compared to healthy smokers. COPD comprises a broad range of features, including emphysema, chronic bronchitis, asthmatic features, and acute exacerbations in COPD (AECOPD). We hypothesized that some of these features of COPD represent a higher risk of lung cancer and non-pulmonary cancer.

Aims:

1. To explore if emphysema and airway wall thickness assessed quantitatively on CT increase the risk of lung cancer and non-pulmonary cancer.
2. To investigate if acute exacerbations in COPD are associated with the risk of lung cancer, and to see whether this association differs based on coexisting asthma.
3. To examine and compare two lung cancer screening scores in our population of patients with COPD.

Materials and Methods: Participants included in the analyses of all three papers were from the GenKOLS study in Bergen, Norway, conducted between January 2003 and January 2005. Participants were 40-85 years of age and had a smoking history of at least 2.5 pack-years at baseline. GenKOLS was conducted as a case-control study. COPD was diagnosed when post-bronchodilator FEV_1/FVC was <0.70 and FEV_1<80% predicted. Baseline examinations included a detailed questionnaire on smoking habits, respiratory symptoms, and disease history, as well as pulmonary function tests. Approximately half of all the participants had a chest CT scan. Baseline data were linked to incident cancer data from the Cancer Registry of Norway throughout the year 2013. All subjects with a cancer diagnosis before inclusion were excluded from the analyses. In Paper III, the subjects were divided into high and low risk according to the National Lung Cancer Screening Trial (NLST) inclusion criteria, and the COPD-Lung Cancer Screening Score (COPD-LUCSS). Cox proportional hazards regression were used to

examine the hazard ratios (HR) for the effect of the predictor variables on the risk of cancer.

Results:

1. After adjustment for age, sex, pack-years, age of onset of smoking, smoking status at baseline, and FEV_1, the baseline amount of emphysema remained a significant predictor of the incidence of non-pulmonary cancer and lung cancer. Airway wall thickness did not predict cancer independently.
2. AECOPD was significantly associated with lung cancer during ten years of follow-up only in COPD patients without asthma. The analysis was adjusted for sex, age, smoking variables, FEV_1, and BMI.
3. The NLST selection criteria, and the COPD-LUCSS were both significantly associated with the risk of lung cancer. The area under the curve values showed that both models have poor discriminatory abilities in our cohort. There was no significant difference in the discriminatory ability between the scores.

Conclusions: Some features of COPD were significantly associated with the risk of lung cancer, and even non-pulmonary cancer. Emphysema was significantly associated with lung cancer risk and risk of non-pulmonary cancer, whereas airway wall thickness was not. AECOPD was associated with an increased risk of lung cancer only in COPD patients without asthma. Some of these features of COPD might be of use in evaluating those who could benefit from lung cancer screening.

Although both the NLST selection criteria and the COPD-LUCSS, were associated with an increased risk of lung cancer, both scores had poor discriminatory abilities in our cohort of COPD patients. More studies are needed to find better models to target those at higher risk of lung cancer.

List of Publications

Paper I

Gagnat AA, Gjerdevik M, Gallefoss F, Coxson HO, Gulsvik A, Bakke P. Incidence of non-pulmonary cancer and lung cancer by amount of emphysema and airway wall thickness: a community-based cohort. Eur Respir J. 2017;49(5):1601162.

PMID: 28495686

Paper II

Gagnat AA, Gjerdevik M, Lie SA, Gulsvik A, Bakke P, Nielsen R. Acute exacerbations of COPD and risk of lung cancer in COPD patients with and without coexisting asthma Submitted.

Paper III

Gagnat AA, Gulsvik A, Bakke P, Gjerdevik M. Comparison of two lung cancer screening scores among patients with chronic obstructive pulmonary disease: A community study. Clin Respir J. 2019;13(2):114-9.

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Terms and Abbreviations

AECOPD	Acute Exacerbation in Chronic Obstructive Pulmonary Disease
ATS	American Thoracic Society
AUC	Area Under the Curve
AWT-Pi10	A standardized measure of Airway Wall Thickness at an internal Perimeter of 10 mm.
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COPD-LUCSS	COPD – Lung Cancer Screening Score
CT	Computed Tomography
EMT	Epithelial Mesenchymal Transition
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GenKOLS	Genetic COPD study
GOLD	Global initiative of Obstructive Lung Disease

HCRHS	Hordaland County Respiratory Health Survey
HR	Hazard Ratio
HU	Hounsfield Units. A density scale, ranging from -1000 HU (equivalent of air) to + 1000 HU (equivalent of dense bone). Water has a density of 0 HU.
HUH	Haukeland University Hospital
ICS	Inhaled Corticosteroids
kVp	kilo-Volt peak. Beam energy
LDCT	Low Dose CT
LLN	Lower Limit of Normal
MMP	Matrix Metalloproteinase
NLST	National Lung Cancer Screening Trial
NPV	Negative Predictive Value
OR	Odds Ratio
Pack-years	Number of cigarettes smoked per day divided by 20, multiplied with the number of years smoked
PPV	Positive Predictive Value
ROC	Receiver Operating Curve
SES	Socioeconomic Status

SOHAS	Second Oslo and Hordaland Asthma Survey
Voxel	A three-dimensional pixel, or a box. The size of a voxel is decided by the resolution of the image and the slice thickness. A voxel is the smallest part of the lung where individual density measurements can be made using quantitative CT.
%LAA	Percentage Low Attenuation Areas. A measure of the degree of emphysema. Indicates the relative amount of lung voxels that has a density less than a given cut-off. The cut-off used in the analyses of this thesis is 950 HU (%LAA950)

Contents

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease representing a significant burden for individuals and society. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report of 2020, COPD is the fourth leading cause of death worldwide and is expected to be the third in the near future (1). Estimated deaths from COPD in 2015 was 3.2 million people worldwide, an increase of 11.6% compared to 1990 (2). COPD is also a substantial cause of morbidity, and many patients die prematurely from either the disease itself, related complications, or its correlated comorbidities. Comorbidities, defined as the coexistence with other diseases, are often seen in patients with COPD. One of these comorbidities is lung cancer. COPD patients are shown to have an increased risk of lung cancer compared to healthy smokers (3). COPD comprises a wide spectrum of features or phenotypes, including emphysema, chronic bronchitis, asthmatic features, and an acute exacerbation in COPD (AECOPD). Lung cancer is a leading cause of death in patients with COPD (1, 4). Due to a lack of symptoms in the early stages of the disease, lung cancer is often discovered at advanced stages with poor prognosis (5). This has led to an extensive debate on lung cancer screening. Several studies aim to identify individuals at higher risk of lung cancer in smokers (6).

In this chapter, I will shortly present relevant background on COPD, including burden, diagnosis, and different features of COPD. Then I will present current knowledge on some features in COPD related to lung cancer and non-pulmonary cancer, followed by an introduction to lung cancer screening.

1.1. Chronic obstructive pulmonary disease

Permanent respiratory symptoms and airflow-limitation characterize COPD. Symptoms arise due to changes in the airways and the alveoli, usually due to significant exposure to noxious particles or gases, of which smoking is the most important. Other factors include passive smoking, indoor and outdoor pollution, occupational dust, and

chemicals. COPD can also be developed due to genetic predisposition, such as alfa1-antitrypsin deficiency. Dyspnea, chronic cough, and phlegm are the most common respiratory symptoms. COPD comprises a broad range of manifestations that overlap with entities such as emphysema, chronic bronchitis, asthmatic features, and an acute exacerbation in COPD (AECOPD), all of which will be addressed later in this section.

1.1.1. Burden

The worldwide prevalence of COPD varies extensively, mainly due to differences in age and tobacco exposure (7). Differences in diagnostic criteria, study design, and diverse population demographics make it difficult to compare various estimates, such as prevalence (8). The Burden of Obstructive Lung Diseases (BOLD) and other large epidemiological studies have estimated that 384 million persons were affected in 2010, which correspond to a global prevalence of 11.7% (9). In Norway, the number was estimated to be 150 000 persons in 2018, which corresponded to 6% of those above 40 years (10). The total number of affected people worldwide is expected to grow in the coming years due to an increasingly aging population and also due to increasing tobacco consumption in developing countries (11). COPD causes an enormous economic and social burden. In the United States, COPD was estimated to cost 32 billion dollars directly and 20.4 billion in indirect costs in 2010 (12). A Norwegian study from 2009 estimated the treatment-related cost of COPD in Norway in the year 2005/2006 to be 105 million euro (13). In developing countries, the primary cost is related to loss of working ability. Often, not only the person directly affected will need to stop working, but also the family members who take care of the patient (14).

1.1.2. Diagnosis

According to the GOLD report, a COPD diagnosis should be considered in a person who presents with dyspnea, chronic cough or phlegm, or a history of exposure to risk factors (15). A detailed medical history is necessary, and a physical examination is useful to sort out other reasons for the symptoms. Spirometry is needed to make the diagnosis in a clinical setting (16). How spirometry is done and values such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) will be explained in the

Methods section. The measurements are evaluated by comparison to reference values based on sex, age, height, and ethnicity. FEV_1 and FVC are presented as percent predicted of these reference values. A post-bronchodilator $FEV_1/FVC<0.70$ is required to confirm persistent airflow limitation and indicates COPD in a patient with fitting symptoms and sufficient exposure to noxious particles (15).

1.1.3. Features

COPD comprises various clinical manifestations, aspects, features, or phenotypes. According to Han et al., phenotypes of COPD refer to one or more disease features that can distinguish patients suffering from COPD based on clinically significant aspects (17). The Spanish COPD guideline introduced four phenotypes based on exacerbation frequency and dominant clinical manifestations, such as emphysema, bronchitis, and bronchial asthma (18). To this date, there is no worldwide consensus concerning which phenotypes of COPD should be included and how they should be defined. Therefore, I will use the term features when addressing clinical aspects of COPD in this thesis. Chronic bronchitis, emphysema, asthma, and frequent exacerbations can coexist in different combinations. The scientific environment is in continuous development when it comes to investigating different features of COPD and their importance in treatment and pathophysiology.

1.1.3.1. Emphysema

Emphysema is the destruction of the alveoli, the surface in the lungs where gas exchange occurs. Structural changes found in emphysema appear as permanent and abnormal enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of the airspace walls. Emphysema is most commonly seen in patients with moderate to severe airflow obstruction but can also occur in people with little or no airflow obstruction (19). Emphysema is best detected on computed tomography (CT) of the chest. The methodology of CT detected emphysema varies and can be divided into qualitative or visual and quantitative or automated assessed emphysema. Qualitatively assessed emphysema is interpreted visually by trained radiologists, whereas quantitatively assessed emphysema is interpreted by computer software.

1.1.3.2. Chronic bronchitis

Chronic bronchitis is diagnosed by a chronic productive cough for three months in each of two succeeding years, where other causes of chronic cough have been excluded (20).

1.1.3.3. Asthma and asthma-COPD overlap

Asthma is another chronic disease, obstructing the airways. It is separated from COPD because the airflow obstruction often is reversible either spontaneously or with treatment (21). Asthma is characterized by recurrent episodes of wheezing, breathlessness, tightening of the chest, and coughing. Patients with asthma might develop COPD (22). Some of the COPD patients have clinical features similar to those in asthma. This mixed phenotype has been referred to as ACOS (Asthma-COPD Overlap Syndrome) and is defined by features shared with both asthma and COPD (23).

1.1.3.4. Acute exacerbations

An acute exacerbation in COPD can be defined as "an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation" (1). However, there is to this date no consensus as to how AECOPD should be defined. Some definitions are mainly based on symptoms, others on the need for healthcare resources, and some both (24). The definition by Anthonisen et al. is one of the most cited definitions of AECOPD (25). The definition describes three levels of exacerbations based on the presence of symptoms. Type 1, all of the following symptoms present: increased dyspnea, sputum volume, and sputum purulence. Type 2, two of the mentioned symptoms present, and type 3, one of the symptoms, and at least one additional criteria; upper respiratory infection within the past five days, fever without other cause, increased wheezing or cough, and an increase in respiratory rate or heart rate by 20% compared with baseline (25). AECOPD is associated with increased hospitalization and mortality. Viruses and bacteria are thought to cause most exacerbations (26, 27), other reasons are eosinophils and environmental factors.

Some of these specific features might more often coexist with different comorbidities, such as lung cancer.

1.2. Comorbidities

Due to common risk factors like smoking, aging, alcohol, diet, and inactivity, comorbidities such as cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer are often seen in patients with COPD (28). Comorbidities have a significant impact on the prognosis of COPD (29). Risk factors and symptoms of COPD might be shared with some of its comorbidities and serve as a link between COPD and other diseases (30). For instance, the existence of COPD may increase the risk of lung cancer (31). Whether COPD increases the risk of cancer outside the lungs as well remains mostly unknown.

1.2.1. COPD, lung cancer and non-pulmonary cancer

Cancer represents a large group of diseases in which abnormal cells overgrow and possess the ability to invade nearby tissue and distant locations through the blood and lymph system (32). Cancer cells can arise in any part of the body, and cancer is the second leading cause of death globally. Cancer was responsible for approximately 9.6 million deaths in 2018. An estimated 1.8 million deaths occurred due to lung cancer globally in 2018 (33), and 2236 in Norway the same year (34). Extensive evidence supports an association between COPD and lung cancer (4). Even though tobacco exposure is said to be accountable for 90% of all lung cancer cases (35) and represents the leading cause of COPD, lung cancer and COPD coexist more frequently than expected if they were to be independently triggered by smoking (36). Impaired lung function has shown to be associated with increased lung cancer risk, adjusted for smoking (37-39). Emphysema is the strongest known imaging biomarker for lung cancer (37). However, conflicting results exist regarding quantitatively assessed emphysema and the risk of lung cancer (38-41). Also, the relationship between AECOPD and lung cancer, and whether a history of asthma affects this relationship, is not clarified.

Tobacco use is associated with an increased risk of several cancer types (42) and is responsible for an estimated 22% of cancer deaths (42, 43). Smoking is a significant cause of inflammation (44), and chronic inflammation is considered an essential part of lung cancer pathogenesis in COPD patients (45). COPD is considered a systemic disease (46), and the systemic inflammation might imply a higher risk of non-pulmonary cancer in at least some COPD patients. Whether emphysema or airway wall thickness (AWT) is associated with cancer outside the lungs, remains unknown.

1.3. Relevant literature

There was a need for clarification concerning whether some features of COPD are linked to lung cancer and non-pulmonary cancer. We, therefore, performed a literature review examining the associations between CT assessed emphysema as well as AWT and cancer risk. A separate literature review was done examining AECOPD and lung cancer, and summary articles were read regarding the role of asthma and lung cancer.

Recent efforts have been made to identify COPD patients who could benefit from lung cancer screening. Some suggest the use of COPD status, airway obstruction, or CT detected emphysema as risk factors to better target the population at highest risk (47-49). Key literature on lung cancer screening was also reviewed prior to the start of the current thesis.

1.3.1. Features of COPD and the risk of cancer

A PubMed search was performed with the keywords: “emphysema and lung cancer”. This yielded 969 papers from January 2000—June 2016, of which all titles were read. I read the abstracts where the titles contained “emphysema” and “lung cancer”, “COPD” and “lung cancer” or other lung disease and “lung cancer” and downloaded the full text of twenty-eight papers after reading the abstracts. Only nine papers used CT detected emphysema as opposed to patient-reported emphysema, and these were included in the overview of lung cancer and emphysema (Table 1). Searches for cancer outside the lungs and COPD or emphysema were also performed, giving one relevant result by June 2016. One study was found addressing AWT and lung cancer. A PubMed search was

done in February 2020 on "COPD exacerbations and lung cancer," which resulted in 248 papers from 2000—2019. All titles were read, but only seven papers were saved after reading relevant abstracts. Only two were directly relevant.

Conflicting results exist regarding emphysema assessed on computed tomography (CT) and the risk of lung cancer. Several studies have found an increased risk of lung cancer by visually or qualitatively assessed emphysema (41, 50-52), whereas not for automated or quantitatively assessed emphysema (38-40). Several of these were cross-sectional studies examining emphysema and lung cancer at the same time and were not able to conclude regarding cause and effect. Another problem when comparing the studies using quantitative measurements is the lack of a standard protocol for the measurements and a common consensus on how much emphysema is considered normal.

One Danish cohort study (53) found that COPD patients had an increased risk of several smoking-related cancers compared to individuals without COPD. They lacked data on tobacco consumption and were not able to adjust for smoking.

AWT and risk of lung cancer was examined in a case-control study, including 117 matched pairs of lung cancer cases and controls sampled from a screening trial (40). They did not observe any relationship between airway wall thickness and the risk of lung cancer.

Only two studies have examined AECOPD and the risk of lung cancer (54, 55). COPD patients with incident lung cancers had more exacerbations 12 months before baseline in a case-control study from the COPDGene cohort (55). In a study of 433 COPD patients and 279 healthy controls, AECOPD was not related to increased incidence of lung cancer during nine years follow-up (54). Often patients with coexisting asthma have been excluded from COPD studies, which was also the case with the latter study (54).

Table 1. Literature review January 2000—June 2016 on CT derived Emphysema and risk of lung cancer

Author/year (ref), study year, country	Aim	Study design, population, follow-up	Inclusion criteria	Emphysema detection method	Results	Comments
Kishi/2002 (39), 1999, USA	Determine if airways obstruction or emphysema were associated with an increased risk of lung cancer.	Cross-sectional, case-control study sampled from lung cancer screening trial. N=1520	≥50 yrs, ≥ 5 yrs life expectancy, current or quit within 10 yrs, ≥ 20 pack years, no oxygen supplement.	LDCT. Quantitative interpretation. Emphysema as a continuous variable and as 0-4%, 5-9%, 10-14% and ≥15%. Threshold -900HU.	Emphysema was not significantly associated with increased lung cancer. Severe airway obstruction, FEV1<40 % was.	Used logistic regression. 22/24 cancer cases detected at baseline. One year follow-up.
De Torres/2007 (51), 2000-2005, Spain	Evaluate whether emphysema on LDCT of the chest is an independent risk factor for lung cancer.	Longitudinal cohort sampled from lung cancer screening trial. 5 years follow-up. N=1166	≥40 yrs, > 10 pack-year, no symptom of lung cancer.	LDCT. Qualitative. Emphysema as present/absent.	Emphysema, not FEV1 was associated with increased risk of lung cancer.	Used Poisson regression. 17/23 cancer cases detected at baseline, little follow-up.
Wilson/2008 (50), 2002-x, USA	Study lung cancer related to radiographic emphysema and spirometric airflow obstruction in tobacco-exposed persons who were screened for lung cancer using chest CT.	Longitudinal cohort sampled from lung cancer screening trial. Average follow-up 3.7 yrs. N=3638	50-79 years, current smoker, or quit within last 10 yrs, >12.5 pack-years. No personal history of lung cancer, no chest CT last 12 months, body weight ≥ 400 pounds.	LDCT. Qualitative. Emphysema as categorical; <10%, 10-25, 25-50, >50%, or as any/no emphysema.	COPD and emphysema assessed semiquantitatively are related to lung cancer, lung cancer occurs most frequently in patients with both COPD and emphysema	Used logistic regression. Annually contact with subjects, verify with medical records, biopsy-verified lung
Maldonado/2010 (38), 1999, USA	Clarify the relationship between lung cancer, airflow obstruction, and the automated quantification of radiographic emphysema.	Longitudinal cohort. Case-control sampled from a screening trial. 4 yrs follow-up. N=1520	≥ 50 yrs, ≥ 5 yrs life expectancy, current or quit within 10 yrs, ≥ 20 pack years, no oxygen supplement.	LDCT. Quantitative. Emphysema as a continuous and as categories: <5%, 5-9, 10-14, 15+ Threshold -900HU	We confirm a significant association between airflow obstruction, whereas emphysema, quantified by automated methodology, was not an independent risk factor.	Used logistic regression. 29/64 lung cancers detected at baseline.
Gierada/2011 (148), 2002-2004, USA	Determine whether quantitative CT measurements of emphysema and airway dimensions are associated with lung cancer risk in a screening population.	Longitudinal cohort. Case-control sampled from lung cancer screening study. 6 yrs follow-up. N=558, 279 cancer cases and 279 controls.	55-74 yrs, ≥ 30 pack-years, current or quit within the last 15 years.	LDCT. Semiautomatically segmented. Emphysema as present/absent <15%, ≥15%. Threshold −950HU.	Quantitative CT measurements of emphysema but not airway dimensions were weakly associated with lung cancer.	Used logistic regression. Lost the association when adjusting for previously reported COPD or emphysema.

Author/year (ref), study year, country	Aim	Study design, population, follow-up	Inclusion criteria	Emphysema detection method	Results	Comments
Li/2011 (129), 1997-2004, USA	Evaluate how well the clinical diagnosis for emphysema conforms to the CT diagnosis and to assess the accurate contribution of emphysema on lung cancer risk.	Cross-sectional. Case-control sampled from lung cancer screening study. N=1015, 565 cases and 450 controls	Individuals with only low-dose CT scans were excluded. Current smokers, ≥ 20 pack-years.	Standard dose CT. Qualitative and quantitative interpretation. Used categories 0%, 0-<5%, 5-<10, ≥10. Threshold -950HU	The presence of emphysema on CT scan is an independent predictor of lung cancer	Compared the use of clinical emphysema assessment and quantitative CT assessment.
Wilson/2011 (40), 2002-2005, USA	Study the relationship between emphysema, airflow obstruction and lung cancer in a high-risk population.	Case-control sampled from lung cancer screening study. Follow-up between 2002-2006. N=234, 117 cases and 117 controls	50-79 years, current smoker, or quit within last 10 yrs, >12.5 pack-years. No personal history of lung cancer, no chest CT last 12 months, body weight ≥ 400 pounds.	LDCT. Qualitative and quantitative interpretation Categories: 0%, 1-10%, 11-25%, ≥26% Threshold -910HU	Quantitative analysis of low-dose screening CT scans failed to reproduce the association of emphysema, as assessed visually on the same CT scans, with the diagnosis of lung cancer.	Used logistic regression. Pathologically verified lung cancers from screening trial. 70 cancer cases detected at baseline.
Smith/2012 (52), 2001-2009, Canada	Determine the extent to which emphysema on chest CT is associated with lung cancer histology.	Cross-sectional, sampled from lung cancer patients included in a clinical database. N=498, all cases	All lung cancer patients from 2001 to 2009 with complete data on age, sex, smoking history, histology and staging chest CT.	LDCT. Qualitative. Emphysema as present/absent and graded: 0%, 1-10%, 11-25%, 26-50%, >50%	Emphysema is associated with significantly increased odds of squamous carcinoma, not small cell carcinoma after adjustment for smoking.	Examined emphysema and types of lung cancer.
Wille/2016 (63), 2004-2006, Denmark	Compare the occurrence of visually detected emphysema and interstitial abnormalities in subjects with and without lung cancer in a screening population of smokers.	Longitudinal study sampled from CT arm of a prospective randomized controlled screening trial. 4 yrs follow-up. N=1990	50–70 yrs, ≥ 20 pack years. Current or former smokers. No known pulmonary disease. FEV1 ≥ 30% predicted.	LDCT. Qualitative and quantitative interpretation. Categories: 0%, <5%, 6-25%, 26-50%, 51-75%, 76-100%. Threshold -950HU	Visual assessment of emphysema is associated with lung cancer risk. Quantification of emphysema by software was less useful.	Used logistic regression. 15/70 lung cancers diagnosed at baseline.

One study examining risk factors for lung cancer in COPD found that coexisting asthma had a protective effect. This study did not adjust for pack-years of smoking, nor lung function, which can explain reduced lung cancer risk with coexisting asthma (56). Studies exploring asthma and lung cancer risk in non-COPD populations have given conflicting results. One meta-analysis found that self-reported asthma increased the risk of lung cancer, whereas a doctor's diagnosis did not (57).

1.3.2. Lung cancer screening

In the 1980s, it was concluded that screening for lung cancer with sputum cytology and chest radiography did not improve mortality (58, 59). Due to these findings, there was a long break in lung cancer screening research. In 1999, chest CT was used for diagnosis and led to a new interest in the field (60). Most clinicians agree that early detection of lung cancer is beneficial, but it remains unclear whom to screen, how often, and how to follow up. A large proportion of false-positive findings and high costs are among the challenges (61). In November 2017, Oudkerk et al. published a European position statement on lung cancer screening (61). They stated that a correct selection of a target population was essential and that the population could not be selected based on age alone, as in many other cancer screening programs. This was due to substantial risk factors such as tobacco smoke. Most randomized control trials (RCTs) performed between 2002—2014 (62-70) had recruitment criteria exclusively based on age and magnitude of tobacco smoking. Wille et al. (63) included FEV_1>30% and performance status in their recruitment criteria but did not find that CT screening improved lung cancer mortality. Field et al. included a risk score for lung cancer incidence based on several factors (69). Since most RCTs based on age and smoking consumption alone have given conflicting results, many multivariable risk prediction models have been published (71-74), trying to improve predictive abilities. None of the RCTs, nor these prediction models, were made in a population of COPD patients, even though several features in COPD are known to increase the risk of lung cancer (3, 51).

1.3.2.1. The NLST and the COPD-LUCSS

To determine whether low-dose CT could reduce lung cancer mortality, the NLST (66) enrolled 53 454 participants at high risk of lung cancer at 33 different medical centers in the United States from August 2002 through April 2004 (66). The participants were randomly assigned to either undergo three annual regular chest X-rays or three annual CT scans. Data on lung cancer cases and lung cancer deaths were collected through 2009. Inclusion criteria were based on age and smoking history and will be presented in the Methods section (Table 4). The NLST observed that the use of low-dose CT (LDCT) reduced lung cancer mortality by at least 20%. Even though the NLST concluded that their data alone were not sufficient to fully inform important decisions on whether or not to recommend screening, some guidelines on screening programs recommend using LDCT of the chest mainly based on the results from the NLST (75).

Several studies have tried to improve the screening criteria since the results from the NLST were published (73, 74, 76, 77). De Torres et al. created a lung cancer screening score for COPD patients, COPD-LUCSS, and validated and compared it to the NLST selection criteria in another population (76). Their score included information on body mass index (BMI), pack-years, age, and emphysema (Table 4). They concluded that their score predicted lung cancer in patients with COPD better than the NLST selection criteria. De Torres et al. compared their score to the NLST selection criteria by visual comparison of Kaplan-Meier plots without an objective statistical test. They did not present the discriminatory abilities of either two scores (76).

1.4. Summary of introduction

In summary, there was a need for clarification concerning the association between different features of COPD and lung cancer risk. We hypothesized that emphysema and AWT increased the risk of lung cancer. With COPD being considered a systemic disease, we further hypothesized that emphysema and AWT were associated with increased risk of cancer outside the lungs as well. We also hypothesized that AECOPD

was associated with lung cancer risk, and that there was a difference in the effect of AECOPD on lung cancer based on coexisting asthma.

After the publication from the NLST by Aderle et al., lung cancer screening was recommended by several guidelines despite numerous unsolved problems. De Torres et al. claimed to have found an improved lung cancer screening score for COPD patients. Both the NLST selection criteria and the COPD-LUCSS need to be evaluated objectively in a more representative COPD population.

We had access to a community-based cohort of subjects with and without COPD with detailed information regarding smoking habits, lung function, disease history, and quantitatively interpreted CT scans of the chest. These data were linked to reliable incident cancer data with ten years of follow-up, enabling us to examine the following objectives.

2. Objectives

Paper I

To investigate if level of emphysema and AWT assessed quantitatively on CT independently predicted subsequent incidence of non-pulmonary cancer and lung cancer.

Paper II

To explore whether an acute exacerbation in COPD was associated with an increased risk of lung cancer, and to examine whether the effect of AECOPD on lung cancer differed based on coexisting asthma.

Paper III

To examine and compare the discriminatory ability of two lung cancer screening scores, the COPD-LUCSS and the NLST criteria, in a cohort of COPD patients.

3. Methods

This thesis is based on data from the GenKOLS study conducted in Bergen, Norway, between 2003 and 2005. Details on the study population, study design, and data management will be presented, followed by key information about the main variables, and an introduction to the statistical analysis done in all three papers.

3.1. Study population and study design

The GenKOLS study took place at Haukeland University Hospital (HUH) and was sampled as a case-control study to examine genetic and environmental factors in COPD. Cases had COPD, defined as post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted. Controls had post-bronchodilator $FEV_1/FVC \geq 0.70$ and $FEV_1 \geq 80\%$ predicted. The examination at baseline in 2003/05 included an extensive questionnaire, including questions on smoking habits, respiratory symptoms, and disease history. Participants performed pulmonary function tests, and about half of them did an optional CT scan. The data from GenKOLS were linked to data from the Cancer Registry of Norway (78) with complete data from 2003 through 2013. The prospective study design enabled us to investigate variables at baseline and effect ahead in time.

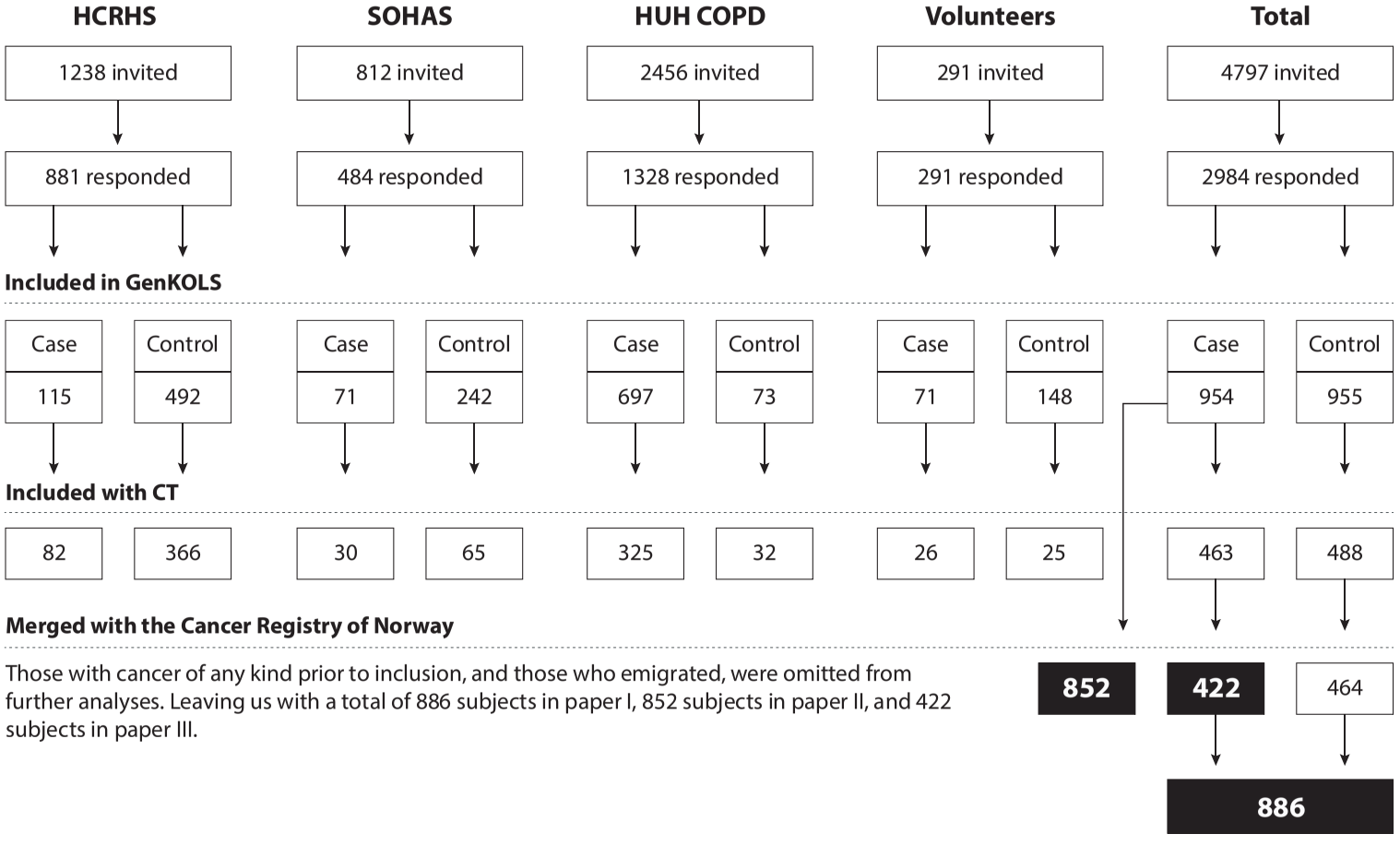
The subjects included in the analyses of Paper I consisted of cases and controls that had a chest CT examination (Table 2). For Paper II, we included all cases. And finally, in Paper III, the sample was restricted to cases with a chest CT.

3.1.1. The GenKOLS population (Table 2) came from four sources (79)

1. Hordaland County Respiratory Health Survey (HCRHS)
2. Second Oslo and Hordaland Asthma Survey (SOHAS)
3. Haukeland University Hospital COPD registry (HUH COPD registry)
4. Volunteers who contacted the staff and wished to join

The HCRHS was conducted in 1985 and was a large population cohort based on simple randomization of the population between 15 and 70 years old in Hordaland county, Norway (80). Those still living in Bergen and surrounding municipalities were invited to participate in one follow-up in 1996 and another follow-up in 2003-2005 (81, 82). The participants who fulfilled the GenKOLS inclusion criteria were invited to participate there as well. SOHAS was performed in Oslo and Hordaland county in 1998 and was a cross-sectional study, including a random sample of inhabitants aged 15-70 years (83). The HUS COPD registry included all patients registered with a COPD or an emphysema diagnosis between 1997 and 2005. The group of volunteers was people who themselves contacted the study staff and expressed an interest in participating.

Table 2. Flow chart of GenKOLS and the participants of Paper I, II, and III



Those with cancer of any kind prior to inclusion, and those who emigrated, were omitted from further analyses. Leaving us with a total of 886 subjects in paper I, 852 subjects in paper II, and 422 subjects in paper III.

3.1.2. Inclusion and exclusion criteria in GenKOLS

Inclusion criteria

- Able and willing to sign an informed consent form.
- Age ≥ 40 years.
- Current or ex-cigarette smoker, minimum 2.5 pack years.
- No evidence of severe α1-antitrypsin deficiency (ZZ, Z Null, Null-Null, or SZ) assessed by PI type.
- Caucasian – self-reported

Exclusion criteria

- Unable to give informed consent.
- Severe anemia as defined by hemoglobin of the same or < 9.0 g/dl.
- Known HIV, hepatitis B or C infection
- Blood transfusion received within last four weeks.
- Chronic pulmonary disorder other than COPD (e.g., lung cancer, sarcoidosis, active tuberculosis, and lung fibrosis.) Inactive tuberculosis and previous diagnosis of asthma were not an exclusion criterion.
- Status post-lung or other organ transplantation.
- Status post-lung volume reduction surgery.
- Taken antibiotics for respiratory disease within one month or have had a respiratory infection within six weeks of the visit.

Participants who fulfilled transient exclusion criteria such as low hemoglobin or recent respiratory infections were reconsidered for inclusion at a later date.

In this thesis, all subjects with a cancer diagnosis of any kind, before inclusion in GenKOLS, were excluded. Also, those who emigrated during follow-up were omitted from the analyses due to an unknown date of emigration.

3.1.3. Study sequence and data collection

All study participants received an invitation with an explanation of the study, a screening consent form, a screening questionnaire (Appendix A, B), and an appointment for a screening visit and clinical examination at HUH (79). At the screening visit, information about the study was given, and all participants signed an informed consent form. The screening questionnaires were completed and checked. Weight and height were measured. All participants underwent pre-bronchodilator spirometry, then case-control questionnaire part 1 was filled out before post-bronchodilator spirometry. Based on the spirometry and screening questionnaire, the participants were identified as either cases or controls. Only those who fulfilled the inclusion criteria continued with further examination and signed an additional informed consent form (Appendix C). They answered the case-control questionnaire, part 2 covering smoking history, medical history, and more. The wording was based on previously validated studies (84). The questions that were used in Paper I-III are printed in Appendix D of this thesis. Also, an optional high-resolution CT scan for quantitative analyses was offered until a total of approximately 1000 CTs were taken. These were equally distributed between cases and controls (79).

3.1.4. Data management

The data obtained from questionnaires and clinical tests were recorded on paper and kept in a locked archive before it was punched into an online database. Continuous error-checks were applied to reveal and correct punching errors, such as missing values and values out of range. Details on data management are presented in another thesis (79).

3.2. Variables

3.2.1. Exacerbations

AECOPD was defined as an antibiotic course taken 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?”

3.2.2. Asthma

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?”

3.2.3. Spirometry

A spirometer measures the lung function as the volume of air being inhaled and exhaled in a certain amount of time, enabling a calculation of flow. The measurements in GenKOLS were done using a Vitalograph 2160 Gold Standard Plus (Appendix E), according to the American Thoracic Society (ATS) standards (85). The spirometric measurements were recorded at the screening visit at least six weeks after any airway infections. The participants were not asked to abstain from daily medication (79). Trained technicians conducted the pulmonary function tests. Both pre-bronchodilator and post-bronchodilator tests were conducted. The post-bronchodilator tests were performed 30 minutes after receiving 400 microgram Salbutamol via metered-dose inhaler and Aerochamber spacer. Three acceptable maneuvers were recorded, and the highest values were selected.

Two parameters were evaluated from spirometry, the FVC, and the FEV_1. The FVC refers to the amount of air that by force can be exhaled from the lungs from a point where the lungs are maximally filled. The FEV_1 is defined as the amount of air exhaled the first second. In healthy lungs, the amount of air forced out the first second represents a large portion of the total FVC. When lungs are obstructed, as in COPD, less air can be forced out in the first second. The measurements are evaluated by comparison to reference values based on sex, age, height, and ethnicity. FEV_1 and FVC are presented

as % predicted. Local reference values for FVC and FEV_1 were used (80). The post-bronchodilator values were used in the statistical analyses.

3.2.4. CT, emphysema, and AWT definition

The high-resolution CT images were acquired at Haukeland University Hospital with a GE LightSpeed Ultra CT scanner (120 kVp, 200 mA; GE Healthcare, Milwaukee, WI, USA) at full inspiration using 1.25-mm slice thickness at 20 mm intervals from the apex to the base of the lung (Appendix F). The quantitative analysis of the CT images was performed by the iCapture Centre in Vancouver, BC, Canada, under the supervision of Dr. Harvey Coxson (UBC James Hogg Research Centre and Vancouver General Hospital). Details on the CT scanning are presented in another thesis (79). The extent of emphysema was assessed quantitatively by a software developed by the iCapture Centre and was obtained using the percentage of lung voxels with X-ray attenuation values below – 950 Hounsfield units (HU). HU represents a density scale, ranging from -1000 HU (the equivalent of air) to + 1000 HU (the equivalent of dense bone). Water has a density of 0 HU. The – 950 HU has shown to be appropriate for measuring emphysema with this CT acquisition technique (86). The term %LAA (percentage low attenuation areas) was used to describe these low-density regions. The percentage of emphysema for the whole lung was calculated. The AWT was calculated by taking the square root of the wall area for each measured airway, plotted against the internal perimeter of that airway. AWT was presented for a standardized airway with an internal perimeter of 10 mm, AWT-Pi10 (87). Details on AWT are presented in another thesis (79).

3.2.5. Lung cancer screening scores

In Paper III we divided the sample into groups of high and low risk according to two different screening scores.

Table 4. Variables included in the COPD-LUCSS (76) and the NLST selection criteria (66).

COPD-LUCSS	
BMI <25	1 point
Pack-years history >60	2 points
Age >60 years-old	3 points
Radiological Emphysema: yes	4 points
Total	10 points

COPD-LUCSS: Chronic Obstructive Pulmonary Disease – Lung Cancer Screening Score
The low risk category included those with 0-6 points. The high risk category includes those with 7-10 points.

NLST inclusion criteria
Pack years >30
Age 55-74 years.
Current smoker or quit smoking within the previous 15 years

NLST: National Lung Cancer Screening Trial
Those with all the mentioned criteria are considered as high risk. Those with two or less of the mentioned criteria are considered low risk.

3.2.6. Norwegian national identity numbers

Every person registered in the Norwegian National Registry has a national identity number of 11 digits. It is a personal identifier that each person receives from birth or when they settle in Norway (88). This number follows the person in all hospital visits and is used in several national registries. This number enabled us to combine data from different registries.

3.2.7. Cancer Registry of Norway

Lung cancer was the primary outcome in all three papers, and non-pulmonary cancer a primary outcome in Paper I. Cancer diagnosis were obtained from the Cancer Registry of Norway (89). The Cancer Registry of Norway was established in 1952 and has since then systematically collected cancer occurrence in Norway. The registry is considered to be close to complete from 1953, and a data quality study found 98.8% completeness for the period 2001–2005 (78). In September 2019, the incidence registry contained information on 1 984 415 cases in 1 574 700 individuals (34). The Cancer Registry also receives data from the Cause of Death Registry to ensure the validity of the data and register new cases first diagnosed after death. In this thesis, lung cancer was defined by

ICD-10-code C34, and non-pulmonary cancers were defined as all cancers outside the lung. We obtained data from January 2003 through December 2013 for the study participants. Data included cancer histology and the time of diagnosis.

3.2.8. Norwegian Cause of Death Registry

All deaths in Norway are registered in the Cause of Death Registry, run by the Norwegian Institute of Public Health (90). We received data from January 2003 through December 2013 for the participants in our study.

3.3. Statistics

All analyses were performed with STATA (Stata Statistical Software: release 13-16; StataCorp, College Station, TX, USA). The two-sided significance level was conventionally set to 0.05 for all analyses in all three papers.

3.3.1. Paper I

AWT measured as AWT-Pi10 and emphysema measured as %LAA were the main predictors of interest when investigating the risk of lung cancer and non-pulmonary cancer. With the lack of a suggested classification of %LAA stages, the degree of emphysema was categorized in the same way as in another paper from our group using the same cohort (91). The emphysema groups were based on visual inspection of a quantile plot. Most participants had %LAA under 3% (60%). A rise occurred between the 60^{th} and 80^{th} percentile, and a steep rise was seen from the 80^{th} percentile. The emphysema groups were, therefore, categorized as follows, low emphysema as %LAA under 3%, medium as %LAA from 3-10%, and high as %LAA above 10%. Low emphysema was considered well within the normal range. The normal range was based on the 95^{th} percentile of the non-COPD participants still alive after a follow-up period (91). Emphysema was also treated as a continuous variable.

Kaplan-Meier plots provided a visual presentation of the emphysema groups and time to a cancer diagnosis (92). We used Cox proportional hazards regression to estimate hazard ratios (HR) for the effect of emphysema and AWT on cancer diagnosis over time. The models were adjusted for sex, age, pack-years, age of onset of smoking, smoking status at inclusion, and FEV_1, which were considered clinically relevant confounders.

3.3.2. Paper II

AECOPD was the main predictor and was analyzed as a dichotomous variable (0 vs. 1 or more exacerbations). Kaplan-Meier methods were used to calculate and plot probabilities for developing lung cancer. We performed Cox proportional hazards regression to quantify differences in the risk of developing lung cancer. In this thesis the hazard ratios are presented as HR, in the submitted paper, we used the term HRR (hazard rate ratio) for the same values (Paper II). We tested for the interaction between AECOPD and asthma on lung cancer to explore whether this effect differed based on coexisting asthma. Relevant covariates were adjusted for in the model, including sex, age, pack-years, age of onset of smoking, smoking status at inclusion, body mass index (BMI), and FEV_1.

To account for mortality as a competing risk, we also performed Fine and Gray competing risk analyses for the probability of developing cancer (93). The Fine and Gray competing risk regression model is often used as an alternative to Cox regression when competing risks are present. In competing-risks regression, the focus is on the cumulative incidence function (CIF), indicating the probability of experiencing an event before a given time. Cox regression, on the other hand, gives estimates for the cause-specific risk (hazard) to have the event (94). In Cox regression, competing risks, such as mortality, are typically censored, and the risk of an event is assumed to be equal for censored and non-censored individuals. In competing risk, a competing risk preceding the event of interest will change the probability of having the event of interest. The results from the Fine and Gray Competing risk model (93) were presented as sub-hazard ratios. We used the Stata command *stcrreg* (94).

3.3.3. Paper III

De Torres et al. (76) claimed to have developed a lung cancer screening score better than the inclusion criteria presented by the NLST, but did not present statistical tests to objectively compare the two scores. We have used several methods to compare the two scores, some of which will require more detailed background information.

An ideal score or model will always be able to classify those who will develop the disease in one category, and those who will not develop the disease in another. A model's ability to do just that can be described by both discrimination and calibration. The discriminatory ability of a model refers to its ability to separate those at high risk from those at low risk of an event (95). Calibration is the model's ability to produce accurate estimates or predicted risks close to the actual observed risk. Both discrimination and calibration are crucial tools to investigate the predictive ability of a model (96). Discrimination for binary events such as lung cancer or no lung cancer can be measured using receiver operating characteristic (ROC) or C statistics. It is, however, important to emphasize that C-index is influenced by follow-up time. The same follow-up time is necessary to compare the C-index in two models (95). The discriminatory ability of both the NLST selection criteria and the COPD-LUCSS was poor in our study. A predictive model with poor discriminatory ability will not be of any use even with proper calibration. Hence, we did not assess calibration herein.

We aimed to examine and compare the discriminatory ability of the two lung cancer screening tools. We did so by dividing the patients into high and low risk groups according to the COPD-LUCSS and the NLST criteria (Table 4) (66, 76). Cox proportional hazards regression was used to estimate HR for the effect of each score on lung cancer risk. Harrell's C concordance statistics estimates were obtained to measure discrimination (97). We used the Stata command *estat concordance* (98). We also used logistic regression with lung cancer as the outcome, with 8 years of follow-up for each participant, to be able to estimate post hoc receiver operating curve (ROC) and intra model area under the curve (AUC) comparisons for the two scores (99). The Stata commands used were *lroc* and *roccomp* (100). This method provided a χ^2-test for the difference in AUCs between the COPD-LUCSS and the NLST. An AUC can vary between 0 and 1. An AUC of 1 indicates a perfect diagnostic tool with 100% sensitivity

and 100% specificity, whereas a value of 0.5 implies no discrimination. We also calculated the sensitivity and specificity, as well as the positive predictive values (PPV) and negative predictive values (NPV), for the two lung cancer screening scores. These terms are commonly used in diagnostic tests and screening settings. Sensitivity is the proportion of positives, correctly identified as that by a test. Specificity is the proportion of negatives, correctly identified as that (101). High sensitivity would mean that a truly sick person would get a positive test. This does not rule out, however, that a healthy person could also get a positive test. In a screening setting, one would be willing to accept some false positives to secure that those with a disease would have a positive screening test. PPV is defined as the proportion of patients with positive test results who are correctly diagnosed, and NPV is defined as the proportion of patients with negative test results who are correctly identified (101). A high NPV is essential in a screening test. We want to be sure that if a test is negative, the person is truly healthy.

3.4. Ethics

Before enrolment in the GenKOLS study, oral and written information was provided, and written, informed consent was collected from all study participants. Data from the Cancer Registry of Norway and the Norwegian Cause of Death Registry were obtained through an application. The projects were approved by the Regional Committee for Medical and Health Research Ethics (REK), REK reference “2010/2575/REK vest”.

4. Main Results

4.1. Paper I

Non-pulmonary cancer was found in 11% of the subjects with a low level of emphysema, measured as %LAA, in 19% with LAA 3–10%, and in 17% of subjects with LAA ⩾10%, during ten years of follow-up. Corresponding numbers for lung cancer were 2%, 3%, and 11%, respectively. The unadjusted hazard ratios showed that older age, pack-years, COPD status, and amount of emphysema at baseline were significantly associated with both incidences of non-pulmonary cancer and lung cancer. FEV_1, in percent predicted, was significantly associated with lung cancer in the unadjusted Cox-regression analysis. In the adjusted Cox regression analyses, the level of emphysema was significantly associated with the risk of non-pulmonary cancer (HR=2.10, 95% CI 1.14-3.87) and the risk of lung cancer (HR=3.33, 95% CI 1.04-10.61). The analyses were adjusted for sex, age, pack-years, age of onset of smoking, smoking status at inclusion, and FEV_1. AWT in terms of Pi10 was not associated with non-pulmonary cancer or lung cancer. We found no relationship between emphysema and the location of cancer or the type of lung cancer.

In summary, quantitatively assessed emphysema was associated with an increased risk of both lung cancer and non-pulmonary cancer, whereas AWT was not.

4.2. Paper II

For the entire sample, 8.8% of the subjects with, and 5.9% of the subjects without AECOPD, were diagnosed with lung cancer. In total, 58 participants (6.8%) were diagnosed with lung cancer during ten years of follow-up. In the adjusted Cox regression model with COPD patients without a history of asthma, AECOPD was significantly associated with lung cancer risk (HR=2.67, 95% CI 1.27-5.58), whereas not for COPD patients with a history of asthma. The analyses were adjusted for sex, age, pack-years, age of onset of smoking, smoking status at inclusion, FEV_1, and BMI. We found a

significant interaction between asthma and exacerbation status in the adjusted analysis on the entire sample.

In summary, AECOPD is only significantly associated with an increased risk of lung cancer in COPD patients without asthma. There is a significant difference between the effect of AECOPD on lung cancer based on coexisting asthma.

4.3. Paper III

The COPD-LUCSS and the NLST selection criteria were both significantly associated with the risk of lung cancer in our population. The hazard ratios for the high risk versus the low risk groups were HR=3.0 (95% CI 1.4-6.5), and HR= 2.2 (95% CI 1.1-4.5), in the COPD-LUCSS, and the NLST selection criteria respectively. Harrell's C concordance statistic estimates were 0.63 for the COPD-LUCSS and 0.59 for the NLST selection criteria. The AUC values were 0.61 for the COPD-LUCSS, and 0.59 for the NLST selection criteria. Comparing tests found no significant difference between the AUC values of these criteria, p-value 0.76.

In summary, even though both scores were significantly associated with increased risk of lung cancer, the AUC values reveal that both scores have poor discriminatory abilities in this cohort of COPD patients. There was no significant difference between the COPD-LUCSS and the NLST selection criteria.

5. Methodological considerations

Decisions concerning methodological considerations are compromises between available resources and the knowledge and experience that the investigator possesses. In this section, I will present some topics for discussion related to the study design, reliability and validity, and the choice of statistical methods.

5.1. Study design

The GenKOLS study cohort used in these studies was sampled as a case-control study to examine genetic factors in COPD. Therefore, the number of cancers was relatively small in this study compared to studies sampling target populations with cancer. Few cancer cases prevented us from being able to examine associations between emphysema, or AWT, or AECOPD and histological lung cancer types. Also, we were unable to examine emphysema, or AWT and different types of cancer outside the lungs. If the primary goal had been to examine lung cancer in COPD patients when designing the GenKOLS study, we would have wanted to include a control group of never-smokers in addition to the smoking controls. We would also have needed to estimate sample size based on lung cancer cases. The prospective design in this study allowed us to look at risk factors at baseline and outcomes further ahead in time, which is an advantage over a cross-sectional design, where it is impossible to say anything about cause and effect.

5.2. Reliability and validity

Reliability and validity are often explained through a comparison to shooting at a target. The goal is to hit the bull's eye on every attempt. High reliability implies a small spread of bullets (Figure 3, A and D) and refers to the consistency of a measure. If similar results under consistent conditions are produced, the measure has high reliability. High reliability can be translated to low variance. The term validity comprises the closeness of what we believe we measure to what we intended to measure. High validity can be

translated to low bias. As shown in Figure 3, both high reliability and validity are necessary to trust the results (102).

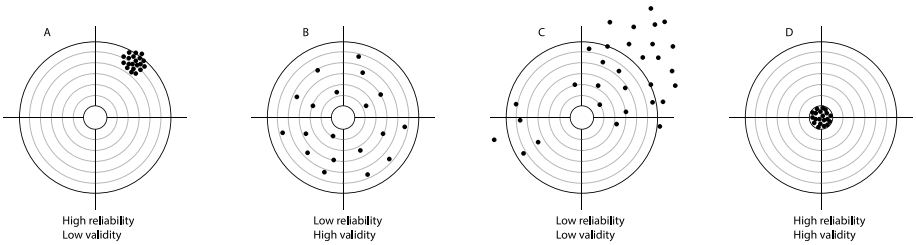


Figure 3, Reliability and Validity

5.2.1. Reliability in GenKOLS

This thesis presents data on pulmonary function, smoking habits, quantitative CT measurements, history of asthma, exacerbations, mortality, and cancer diagnosis.

Pulmonary function tests were done using standardized spirometry equipment (Appendix E). ATS guidelines from the time of inclusion were followed (85). These guidelines provide recommendations on test performance and quality control, contributing to high reliability.

We used self-reported data on smoking habits, history of asthma, and exacerbations the previous year. Questionnaires are susceptible to inaccuracies due to poor recollection of older data or misinterpretation of the questions. Also, weak data handling afterward can be a problem. The wording of the questions used was based on validated studies (84), and precautions such as quality control and inconsistency analyses of the data entering were done to secure correct data handling (79).

The CT images were taken according to the manufacturer's recommendations with standard equipment (Appendix F). Internal repeatability tests were not done to avoid further radiation risk. The quantitatively assessed CT scans were interpreted by a few trained operators and could, to a certain degree, be operator dependent. Analyses of a

randomized sub-sample of 20 subjects whose CT were interpreted by two different operators showed a good correlation between the quantitatively assessed measurements. The mean absolute difference between the two operators' %LAA-values was 0.005 (range 0.00-0.03) (79).

Data on mortality and cancer came from national registries with a high attendance rate. The mortality data used in this thesis was limited to all-cause mortality preventing any bias from the cause of death. The Cancer Registry of Norway has high reliability and validity (78).

In summary, low reliability results in high variance and low statistical power. We were able to achieve high reliability for most of our variables. The inaccuracies of the AECOPD diagnosis might have led to lower statistical power when examining the relationship between AECOPD and lung cancer and will be addressed later in this section.

5.2.2. Validity in GenKOLS

Validity is commonly divided into internal and external validity. Internal validity expresses the ability of a study to draw valid conclusions regarding the study population. In epidemiological studies, validity includes selection bias, confounding, and information bias. External validity refers to how applicable the findings are to the general population at large.

5.2.2.1. Selection bias

Selection bias can be defined as bias resulting from methods used to select the participants and from factors influencing the participation in the study (103). Selection bias is a potential problem if the prevalence of outcomes or predictor variable varies amongst those who respond and those who do not.

In this study, 57% of the included subjects were sampled from population-based cohorts (104, 105), whereas 38% of the subjects came from the COPD patient registry at HUH.

The volunteers comprised 5% of the included subjects. Subjects from the patient register had lower lung function, were older, and had more comorbidities than cases from the general population (106). 4797 subjects were invited to attend the GenKOLS study, of which 62% attended the screening visit. 1909 fulfilled the inclusion criteria and were included in the study. The leading causes of non-response were unwillingness (14%) or feeling too ill to participate (14%), 1% lived outside Hordaland County, and 8% are unknown. More women than men were non-responders compared to the responders, and the non-responders were older than the responders (106). In addition to older age, one may expect more smoking in the non-responders and thus possibly a higher cancer incidence. A possible effect could be an underestimation of the effect of emphysema and AECOPD on risk of lung cancer and non-pulmonary cancer. On the other hand, we might expect the cancer incidence to be higher in the patients registry, compared to the general population, due to age (107), and therefore a corresponding overestimation of the effect of emphysema or AECOPD on risk of cancer.

Half of the subjects underwent a CT scan (951/1909). The CT scan was an optional examination due to the radiation risk and was not a random selection. The examination was offered to the GenKOLS participants until there were approximately 500 cases and 500 controls who had a CT scan. There were no obvious differences between the participants with and without a CT scan regarding age, sex, smoking habits, lung function, or lung cancer incidence (Table 5). Hence, we think that the fact that only half the GenKOLS sample underwent CT thorax examination, may not have influenced the observed associations between the levels of emphysema and airway wall thickness, and cancer.

Table 5. Comparison of GenKOLS subjects with and without CT

	GenKOLS (all)		GenKOLS (no CT)		GenKOLS (CT)	
	No COPD	COPD	No COPD	COPD	No COPD	COPD
N	890	852	426	430	464	422
Male (%)	50	62	47	59	54	64
Age (Mean)	55	65	55	66	55	64
Currently smoking (%)	41	46	41	43	42	49
Pack-years (Median)	16	28	16	29	16	27
FEV1 % pred (Mean)	95	51	95	49	95	53
Lung Cancer (%)	1	7	1	7	1	7

The mortality and cancer data came from national registries (89, 90) with no room for selection bias.

5.2.2.2. Confounding

A confounder is a variable (known or unknown) that influences both the predictor and the outcome (Figure 4, A).

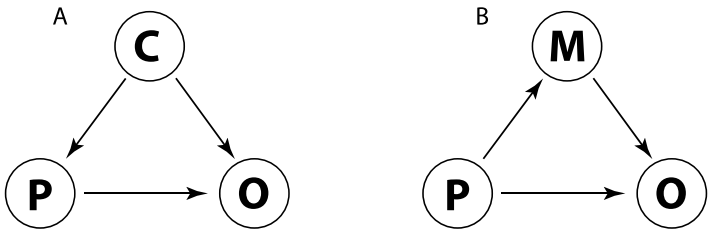


Figure 4. A: Confounder, B: Mediator
P = predictor, O = outcome, C = confounder, M = mediator

Known and measured confounders can be adjusted for in the statistical analyses. An obvious confounder when examining COPD and the risk of lung cancer is smoking, which causes both COPD and lung cancer. This study did not include never-smokers, which prevents us from generalizing the findings to a never smoking population. Moreover, we cannot exclude the possibility of residual confounding due to smoking. Subjects with tobacco consumption as low as 2.5 pack-years were, however, included.

We had access to three different smoking variables, which were all adjusted for in Paper I and II. Age of onset of smoking might be important due to different susceptibility to epigenetic changes when starting to smoke early in life (108, 109). The acute effect of smoking might effect both development of emphysema and lung cancer (110), we therefore adjusted for smoking status at inclusion to examine the effect of emphysema, adjusted for the acute effect of smoking. We did, however, not know the smoking status at the time of the cancer diagnosis, which prevents us from fully adjust for the acute effect of smoking. Number of cigarettes smoked is also a known risk factor for both COPD (111) and lung cancer (112) and was expressed as pack-years.

Lower lung function is associated with increased risk of lung cancer (37-39) and emphysema might lead to lower FEV_1. However, lower FEV_1 does not generate emphysema. This makes FEV_1 a mediator and not a confounder (Figure 4, B). By adjusting for a mediator, one examines the effect on the outcome that does not go through the mediator. In Paper I, we adjusted for FEV_1 in our analyses, knowing that the effect we see from emphysema on lung cancer and non-pulmonary cancer is the effect not mediated trough FEV_1. In Paper II, we adjusted for FEV_1 when examining the association of AECOPD and lung cancer risk. We know that lower FEV_1 indicates more frequent exacerbations (113) and that exacerbations can lead to a quicker decline in FEV_1 (114, 115). We adjusted for FEV_1 to avoid estimating the effect of lung function on the risk of lung cancer.

Patients with lung cancer are found to have lower socioeconomic status (SES) compared to subjects without lung cancer even after adjustment for smoking (116). Lower SES might have exposed these patients to several risk factors through work and lifestyle. One way to adjust for SES is through education. We had access to information on the participants' educational level divided into primary school, secondary school, and university. One could argue that the educational level should have been included when examining the risk of lung cancer in COPD patients. Additional adjustment for education did not significantly change the effect size of the predictors in the primary analyses in our study. Other possible confounders such as age and sex were also adjusted

for. In conclusion, we adjusted for the most important confounders in the relationship between COPD and cancer. However, we cannot rule out residual confounding.

5.2.2.3. Information bias

Information bias occurs when there are measurement errors in the data collected that result in different information quality between compared groups (103). Information bias is often divided into non-differential and differential misclassification. The former refers to a misclassification that is probably the same across all study subjects, whereas differential misclassification can appear when the error is more likely in one group. In GenKOLS, that could, for instance, be if patients affected by COPD reported smoking less accurately than subjects without COPD. Questionnaires are vulnerable to inaccuracies. It is, however, similar to a real-life clinical setting where patients also might underestimate smoking consumption. A potential underestimation of tobacco consumption is likely the same in those with cancer compared to those without cancer, at least considering that the participants did not have cancer at the time of inclusion.

The quantitatively assessed CT scans were interpreted by a few trained operators and could, to a certain degree, be operator dependent. However, operators were, blinded to other data, and cancer data used in this study were obtained several years after the CT interpretations. One could, therefore, assume that misclassifications of the measurements were non-differential.

The participants were considered to have asthma if they gave affirmative answers to both: “Have you had asthma?” and “if yes, was this confirmed by a doctor?” The latter question strengthens a true diagnosis, but still depends on the access to a doctor and that the doctor was right. Lung cancer was in all subjects diagnosed after baseline data collection, preventing recall bias. A misclassification of asthma is likely to be non-differential by lung cancer.

AECOPD was based on the questions: “Have you had treatment with antibiotics for lung disease during the last 12 months?” and “If yes, how many times?” It is difficult to know

whether pneumonia was counted as an exacerbation. Previous pneumonia predicts lung cancer in several studies (117) and could be a potential source of bias.

We examined future diseases that the participants, and the study crew did not know about at the time of data sampling. We, therefore, expect potential information bias to be non-differential misclassification.

5.2.2.4. External validity

Results from the HCRHS are considered generalizable for the population in Hordaland County and the Norwegian society at large within the age-range of the study (118). The GenKOLS study was sampled as a case-control study, and not only sampled from HCRHS. In our case, however, it is more interesting to know whether the COPD cases are generalizable to the COPD population at large. 73% of the cases were sampled from a hospital registry. These patients were older, had lower lung function, and had more comorbidities than those recruited from other sources (107). Thus, the disease severity distribution is likely to be somewhat higher than in the general population (107). There was, however, a higher non-response rate for older people, and sicker people from the general population (106), which might help even out the differences.

5.3. Variables

5.3.1. The diagnostic criterion of COPD

At the time of study recruitment, it was common to diagnose COPD in a patient with a post-bronchodilator $FEV_1/FVC<0.70$, fitting symptoms, and sufficient exposure to noxious particles (119). The $FEV_1/FVC<0.70$ cut-off has correlated well with an increased level of respiratory symptoms (120). However, the use of the FEV_1/FVC fixed ratio will likely cause an overdiagnosis of COPD in the elderly and underdiagnosis in younger adults (121). Therefore, some suggest using the fifth percentile lower limit of normal (LLN) of the FEV_1/FVC ratio (122-125). Due to diagnostic simplicity and the limited risk of misdiagnosis and over-treatment with the use of a fixed ratio, the GOLD

report still recommends the fixed ratio to confirm persistent airflow limitation (1). In 2012 new multi-ethnic reference values for spirometry for the age range 3-95 years were published. The authors of the global lung function 2012 equations (GLI-2012) recommend the use of LLN when diagnosing airway obstruction (126). Also, Norwegian pulmonologists recommend the use of GLI-2012 and LLN in COPD diagnosis (127). In our study, some COPD cases would probably be considered controls and some controls would be considered COPD cases with the use of LLN as opposed to a fixed ratio. In Paper I, we aimed to examine the effect of emphysema and AWT on lung cancer and non-pulmonary cancer. Emphysema is also found in some with normal spirometry (19). Since we included both cases and controls with a CT scan of the lungs in the analyses, the definition of COPD would not influence the results. In Paper II, we included COPD patients based on the fixed ratio, which might have led to overdiagnosis in older subjects, compared to the lower limit of normal. In Paper III, we aimed to examine and compare a lung cancer screening score made and validated in a COPD population. We used the fixed ratio to define COPD just like de Torres et al. (76) to best be able to compare our results to theirs.

5.3.2. Emphysema

Several studies (40, 50, 51, 128, 129) found a relationship between qualitatively assessed emphysema and lung cancer, whereas conflicting results exist concerning quantitatively assessed emphysema. The qualitatively assessed method is a potential problem because radiographic characteristics, for instance, nodules, might affect the readers' interpretation of the amount of emphysema, even though they are supposedly unaware of the lung cancer diagnosis (50). The use of quantitative methods would strengthen the argument for an actual cancer risk from emphysema as compared to using a qualitative method.

The CT scans in the GenKOLS study were acquired using a high-resolution CT technique, which was common during data acquisition. A standard protocol was used when performing the CT scans, and the measurements of emphysema have shown to be reproducible using this standard protocol (130). Studies have found that limited CT

scans can produce overall emphysema values comparable to complete volumetric CT scanning (131). The X-ray attenuation cut-off was set to -950 HU for emphysema. This cut-off is accurate for this CT acquisition technique (86). In conclusion, the quantitative CT acquisition used in this study is adequate for the aims of the study.

5.3.3. Airway wall thickness

In our study, the airway wall thickness in terms of Pi10 did not predict the incidence of lung cancer or non-pulmonary cancer. The lack of a relationship between AWT and lung cancer risk is in line with the findings of a previously published case-control study (40). One study was able to show a relationship between AWT and the risk of lung cancer. However, this association was lost when adjusting for lung function, measured as FEV_1 (55).

AWT is anticipated to reflect chronic inflammation in the airways, yet we were unable to show an association between AWT and lung cancer risk. The changes in the airways that cause airflow limitation in COPD are mainly seen in the small airways, <2mm (132). These are difficult to measure with a CT scan, allowing assessment of the central airways. The findings in the central airways are, however, found to correspond to the distal airways (133). Airway wall thickening in COPD corresponds to chronic inflammation, but also structural changes including hyperplasia and hypertrophy of parietal glands, enlargement of goblet cells, and mucus production (134, 135). It may be challenging to determine whether airway wall thickness, as measured by Pi10, reflects active, stable, or burned out disease (136). Hence, the lack of a Pi10 lung cancer association in our study may indicate that Pi10 is an unspecific measure of airway inflammation. Consequently, we cannot rule out that there is an association between airway inflammation and lung cancer, but our methods have not been specific enough to show it.

5.3.4. Asthma in patients with COPD

Clinical studies have found the prevalence of asthma and COPD mixed phenotype in the COPD population to be between 20 and 40% (137, 138). In the GenKOLS population, we found a prevalence of COPD patients with a history of asthma close to 50%, which is in line with other epidemiological studies (139-142). The characteristics of COPD patients with asthma matched other studies in that they had a lower FEV_1, higher exacerbation frequency, and lower tobacco consumption compared to COPD patients without asthma (143). One could imagine an overdiagnosis of asthma in those COPD patients with AECOPD due to misinterpretation of the exacerbation as an asthma attack. The effect on our results would depend on the link between asthma and lung cancer. If the lack of an association between AECOPD and lung cancer in COPD patients with coexisting asthma is due to a protective effect from asthma treatment, a potential misclassification is less likely to affect the results. If asthma itself is a protective factor, and several COPD patients have a wrong asthma diagnosis, this effect might be underestimated. A misclassification of asthma is likely to be non-differential when comparing those with and without cancer.

5.3.5. Exacerbations

It is common to treat moderate to severe exacerbations with either systemic steroids, antibiotics, or both, based on clinical presentation. In our study, we only had information on events that needed antibiotics. Thus, we did not know whether there were some events needing steroid treatment. The numbers of AECOPD were, however, similar to the numbers reported by the similar GeneCOPD study (55). One study by Erdal et al., using the EconCOPD cohort in Bergen, found that the prevalence of AECOPD using a symptom-based AECOPD definition was significantly higher in both a community-based cohort and a hospital register-based cohort compared to a utilization-based definition (144). An underdiagnosis of AECOPD could result in less statistical power in the analysis when examining the association between AECOPD and lung cancer.

5.4. Analytical considerations

5.4.1. Exacerbations

The GOLD guidelines suggest that a history of zero or one exacerbation during the previous 12 months represents a low future risk of exacerbations, while two or more represent a high risk (1). Hurst et al. (145) used the same division when they supported a distinct phenotype, susceptible to exacerbations. They did, however, also find an increased risk of exacerbation occurrence during the first year of follow-up with a history of at least one self-reported exacerbation during the year before inclusion (145). In our study, we divided AECOPD in zero exacerbations versus one or more exacerbations the previous year. We found the same trend in the statistical analyses when dividing AECOPD in zero, one, and two or more, however, not significant. The lack of a statistically significant association between two or more AECOPD and lung cancer could be due to small numbers and weak statistical power.

5.4.2. Fine and Gray competing risk model

In Paper I and Paper II, Cox proportional hazard regression was used as the primary statistical tool to analyze the risk (hazard) of developing lung cancer. One could argue that Fine and Gray competing risk regression (146), would be more appropriate because this model takes mortality into account as a competing risk (146). When discussing the prognosis of a patient, competing risk can have an impact. Taking the risk of death (or other competing outcomes) into account may influence whether or not to go through with a particular treatment. Hence, for such situations, one could argue that competing risk regression models are better suited for the analysis of risk factors, as opposed to models analyzing the single risk (hazard), as the Cox-regression model does. Still, we argue that using Cox regression is appropriate for the analysis of our data when addressing etiological questions (146). Death as a competing risk increases by increasing age. Therefore, in the Cox model, mortality is indirectly adjusted for through variables included in the analyses linked to mortality, such as age, lung function, and pack-years (147). In Paper II, we performed Fine and Gray competing risk regression as

a supplementary analysis. This regression gave practically the same risk estimates as when using the Cox model.

6. Discussion of main results

6.1. Emphysema and lung cancer

We found a significant association between lung cancer risk and quantitatively assessed emphysema. Several studies have shown an increased risk of lung cancer by visually or qualitatively assessed emphysema (41, 50, 51), whereas not for quantitatively assessed emphysema (38-40). There are several feasible explanations for the discrepancy between our findings and those of other studies. Several of these studies were cross-sectional or had short follow-up time (Table I), making them more vulnerable to bias and preventing them from saying anything about cause and effect. Common for three studies (38-40) using quantitative assessment were the use of an attenuation threshold for emphysema of -900 or -910 Hounsfield Units (HU). A threshold of -950 HU has shown to be appropriate for emphysema (86). One study using -950 HU as a cut-off found a weak association between emphysema and lung cancer. However, they concluded that this was not clinically relevant (148). This study adjusted for previous lung disease, including previous emphysema, which might explain the loss of an association. A recent study found that qualitative assessment was better at discovering mild emphysema in LDCT than quantitative assessment (149). Although emphysema in high resolution CT is found to be comparable to findings in LDCT, the radiation dosage, and the reconstruction of the pictures might affect the results (150). The lack of common standards for quantitative CT assessment and the lack of a suggested classification of %LAA stages make it difficult to compare the studies.

One study showed that patients with mild COPD have the highest incidence of lung cancer (4), which fits with findings on decreased key inflammatory cells in mild COPD (151). Patients with severe COPD might be survivors without predisposing factors for developing lung cancer (152), or might die from competing risks such as heart disease, other types of cancer, or the COPD itself. Survivor bias and competing risks might both explain the lack of an association between emphysema and lung cancer in those

comparing severe emphysema to less severe emphysema. We had access to emphysema measurements in patients with COPD and healthy smokers and were thus able to compare mild emphysema to less than 3% emphysema.

Two recent longitudinal studies including patients with and without COPD, confirm our findings in showing an increased risk of lung cancer with quantitatively assessed emphysema (54, 55). Carr et al. (55) found that both visually assessed emphysema and quantitatively assessed emphysema was associated with lung cancer. They used similar radiation dosage and reference values to emphysema as we did. After adjusting for FEV_1 in addition to age, ethnicity, sex, smoking status, pack-years, and years since quitting, the association between quantitatively assessed emphysema and lung cancer was lost. Some effects of emphysema on lung cancer might be mediated through FEV_1. Thus, adjustment for FEV_1 affects the association. Carr et al. had a shorter follow-up time, with 10% of the participants having no follow-up time at all. They state that they expect some of their lung cancers to be unreported (55). In several studies, the authors either detected lung cancers themselves during follow-up (39, 51) or were depending on obtaining information from the patients (50) and death certificates (55). We had histologically verified lung cancer diagnosis in more than 90% of the lung cancers, which strengthens our results. Figure 5 shows the distribution of histological lung cancer types found in Paper I and Paper II.

Husebø et al. (54) examined several risk factors in COPD and lung cancer in a population, which included some of the same participants as in GenKOLS, sampled later in time. They were also able to show an increased risk of lung cancer by quantitatively assessed emphysema (54). There are several possible mechanisms linking emphysema and lung cancer.

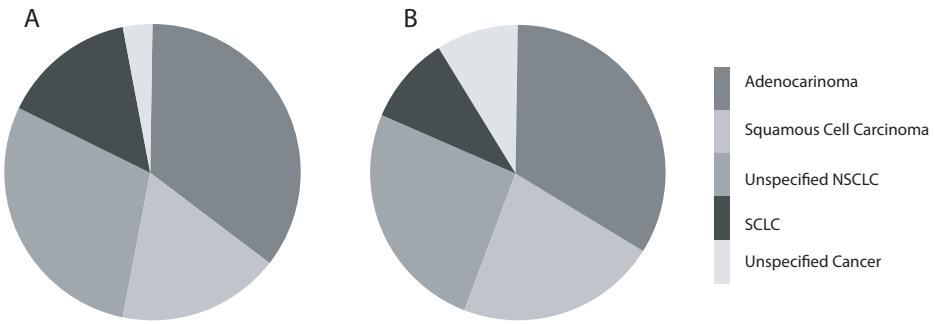


Figure 5. Distribution of histological lung cancer types in Paper I (A) and Paper II (B)

First, inflammation is fundamental in lung cancer pathogenesis in COPD patients (45) and is also present in COPD patients with emphysema (153). Pulmonary emphysema works to create a tumor-friendly environment (154). Murakami et al. (154) found overexpression of matrix metalloproteinase 9 (MMP-9), a collagenase that can facilitate tumor invasion and metastasis in mice with emphysematous lungs. The expression of MMP-9 in intratumoral stromal cells was also associated with more aggressive lung cancer and was mostly found in tumors from lungs with emphysema (154). One study from 2018 by Kerdidani et al. discovered that cytotoxic T cell responses against developing lung cancers are dramatically impaired by emphysema (110). Emphysema impacts antitumor T cell responses to a critical point at which nascent cancer cells escape immunity and grow unaffected (110). The authors proposed that suppression of adaptive immunity against lung cancer links emphysema and COPD to lung cancer and suggested emphysema patients to be candidates for cancer immunotherapies (110).

Second, COPD patients who have smoked have a higher risk of lung cancer than healthy smokers (3). Tobacco exposure induces several mechanisms, such as oxidative stress, chronic inflammation, and epigenetic changes. The repetitive lung injury contributes to a shorter lifespan in lymphocytes. It damages the DNA of lymphocytes in smokers in general and even more in COPD (155, 156), which weakens the immune response and causes an inability to remove transformed or mutated cells. Thus, increasing the susceptibility to respiratory infections and cancer in COPD patients (157, 158).

COPD patients that are never smokers (159) and patients with alpha-1 antitrypsin deficiency who have not smoked (160) also have an increased risk of lung cancer. This implies that the effects of emphysema and COPD mentioned above might be relevant even if not induced by tobacco exposure. Also, not all who are exposed to tobacco develop COPD or lung cancer. Thus, one expects a particular susceptibility to disease in a subgroup of smokers.

Third, the link between emphysema or COPD and lung cancer might lie in the genetics or epigenetics (37). CDKN2A is a shared methylation link between lung cancer and COPD, which encodes for tumor suppressors p16 (INK4A) and p14 (ARF) (161). This fits with both lung cancer and COPD being considered as diseases of aging (36, 162). One study found that immune genes expressed by either tumor cells or tumor-infiltrating immune cells in COPD patients were more methylated than those from patients without COPD (163). Some of the loci that regulate susceptibility for COPD in smokers might also determine susceptibility to lung cancer. This theory is supported by genome-wide association studies identifying several overlapping loci (164-166). The rs7326277TT genotype in VEGFR1 is a vulnerable locus in both diseases and promotes epithelial mesenchymal transition (EMT) and tumor growth (167). In EMT epithelial cells lose cell-cell adhesion. The cells produce segments of extracellular matrix and gain mesenchymal traits of invasion and migration (168). Thus, COPD may epigenetically adjust the immune response and, therefore, increase the risk of both lung cancer and cancer outside the lungs.

Fourth, other environmental factors such as exposure to metals and dust might cause both emphysema and malignancies (169). Asbestos is found to induce emphysema (170) and both pulmonary and non-pulmonary cancer in heavily exposed individuals (171). Another example is inhalable quartz, which is associated with COPD (82) and can be involved in lung cancer development (172). Work dust might enhance lung cancer development in smokers (173), whether work dust causes an additional enhancement of cancer development in patients with emphysema, remains unknown. Urban particulate

matter also increases the risk of lung cancer (174) and is associated with the prevalence of COPD (175).

Risk factors such as indoor biomass fuel (176), and outdoor air pollution, play an important role in the development of COPD (177) and lung cancer, especially in low-income countries (178). A large commission reviewing the evidence for an association between household air pollution and various respiratory diseases reported that household air pollution was associated with both COPD and respiratory tract cancer, including nasopharyngeal cancer and lung cancer (179). This review reported formaldehyde, benzene, arsenic, and nickel in the wood and coal in the household fumes, which are all carcinogenic to human beings (179). Biomass is also associated with COPD. Like tobacco, biomass from plant material generates carbon-based particles covered with polycyclic hydrocarbons and irritant gases such as formaldehyde (179). It is unclear whether COPD from biomass represents a different phenotype than tobacco-induced COPD and, therefore, imposes a different lung cancer risk.

Fifth, the airways are inhabited by bacteria, viruses, and fungi, which comprises the lung microbiome (180). The microbiome might change due to smoking, air pollution, or other irritants, causing damage to the immune system (181), possibly making the lungs more susceptible to cancer. To this date, the role of the lung microbiome in COPD continues to be uncertain. Data are inconsistent, and results across studies are difficult to reproduce (182). Nevertheless, the microbiome in the airways of COPD patients is different from healthy controls (183). We do not know whether there are microbial profiles associated with lung cancer. Studies on the microbiome in colon cancer have shown that bacteria such as Bacteroides fragilis and Fusobacterium nucleatum enhance tumorigenesis and regulate the tumor-immune microenvironment (184). One recent study showed an exclusive bacterial signature in persons with lung tumors containing TP53 mutations (185). One might hypothesis that the microbiome in emphysematous lungs increases susceptibility to lung cancer or enhance lung cancer progression.

6.2. Emphysema – and non-pulmonary cancer

This study is the first to show that emphysema detected quantitatively on CT is associated with an increased risk of non-pulmonary cancer. One Danish study found an increased risk of smoking-related cancers in COPD patients but was unable to adjust for smoking (53). We had access to pack-years, age of onset of smoking, and smoking status at inclusion. A recent Japanese retrospective study examining airflow obstruction in patients with urothelial cancer found that levels of emphysema were significantly higher in those with airflow limitation and urothelial cancer than in those with airflow limitation alone (186).

It could be that the effect of emphysema on non-pulmonary cancer in our study is mainly driven by smoking-related cancers such as urothelial cancers, as seen in the study by Naka et al. (186). We found an increased risk of non-pulmonary cancer, by amount of emphysema when examining non-pulmonary cancer as one group. We did, however, not have sufficient statistical power to examine the association of emphysema and different cancer types outside the lung. However, in the high emphysema group, 20% of the cancers were urinary tract cancers, whereas only 8% were urinary tract cancers in the low emphysema group (Table 2, Paper I). There might be several explanations for the association between emphysema and cancer outside the lungs.

First, COPD and emphysema are associated with increased inflammation in the lungs (153). Several theories exist as to why patients suffering from COPD also have increased systemic inflammation. One is that the lung inflammation causes a “spillover” of inflammatory markers into the circulation resulting in immune reactions in the extrapulmonary organs (29). Inflammatory mediators such as chemokines, cytokines, growth factors, free radicals, and enzymes like MMPs are activated in several types of cancer (187). Several of these markers are also increased in patients with COPD (46, 188) and may act to create a favorable microenvironment for the development of tumors (187). Accumulation of inflammatory cells like macrophages in the lung interstitium followed by disruption of alveolar structure and inhibition of the repair processes involving chemokines (CXCL-2), proteases (MMPs), and inflammatory cytokines are part of the pathogenesis in emphysema (189). CXCL-2 also participates in the

oncogenesis of urothelial cancer. MMPs induces EMT and thus regulate tumor growth and invasion in bladder cancer (190). In urothelial cancer, M1 macrophages are related to carcinogenesis by accumulating and inducing inflammation leading to EMT via inflammatory markers such as TNF-alfa, TGF-beta, or IL-6 (191, 192). Similar cytokines are found to evoke chronic inflammation in the airways (189, 193). The spillover of such cytokines might represent a link between COPD and cancer outside the lungs.

Second, emphysema has been considered a marker for accelerated aging in COPD (162). Hence, emphysema may indicate senescence of the lungs, like muscle wasting and osteoporosis in COPD might indicate senescence in other organ systems. Aging is related to increased risk of cancer development (194). As a consequence, both emphysema and increased risk of cancer could be part of an accelerated aging process in patients with COPD.

Third, smoking is also considered to alter aging, and in COPD, comorbidities have been associated with both the smoking itself and the accelerated aging process (195). Not all smokers develop COPD or smoking-related comorbidities. One clinical study showed significantly thicker carotid intima-media, a risk factor for cardiovascular disease, in smokers with airflow limitation compared to smokers without, whereas no difference between smokers and non-smoking controls (196). These results indicate that genetic and epigenetic factors might be relevant when trying to explain why some seem to be more susceptible to smoking-induced inflammation in the lungs and other organs.

There are several chronic diseases with chronic inflammation such as diabetes, rheumatoid arthritis, obesity, and atherosclerosis that are found to have an increased risk of cancer (197-202). Several of these diseases are associated with smoking and smoking-induced inflammation. The same mechanisms that make these smoking-induced chronic diseases associated with cancer might also count for emphysema and cancer.

6.3. AECOPD in COPD patients with and without asthma and lung cancer

We observed a significant association between AECOPD and an increased risk of lung cancer only in COPD patients without asthma. The association was independent of sex, age, BMI, lung function, pack-years, age of onset of smoking, and smoking status.
Few other studies have examined AECOPD and lung cancer. Carr et al. found that incident lung cancer cases had more exacerbations at baseline than those without lung cancer in a cohort of patients with and without COPD (55). This association was no longer significant when examining the COPD cases only. Compared to Carr et al., we had a longer follow-up time and complete cancer data (Paper II). Husebø et al. were not able to show an association between AECOPD and risk of lung cancer (54). They used the Bergen COPD Cohort study, which partly recruited participants from the GenKOLS study. Their inclusion criteria required a higher smoking consumption and a smaller age range. Patients with previous asthma were also excluded. Husebø et al. detected 32 lung cancer cases and did not report the number of exacerbations. The lack of an association in their study could be due to small numbers and low statistical power. Our study is the first to explore if there is a difference in the effect of AECOPD on lung cancer based on coexisting asthma. Several possible mechanisms might help explain our findings.

First, asthma in COPD patients was associated with a lower risk of lung cancer in a recent retrospective study (56). COPD with coexisting asthma might be caused by different mechanisms and represent a distinct phenotype with a reduced risk of lung cancer. There are, nonetheless, essential weaknesses in this study. They lacked information on lung function and tobacco exposure and were unable to adjust for these variables in the analyses (56). COPD patients with asthma might have smoked less and, therefore, have a decreased risk of lung cancer.

Second, increased systemic inflammation is found in COPD patients with frequent exacerbations (54). AECOPD may be induced by various triggers and cause different inflammatory responses (203). In COPD, one often sees a neutrophilic inflammation driven by CD8+ T-cells, whereas eosinophilic inflammation mediated by CD4+ T-cells is more dominant in asthma (204). We lack information on inflammatory markers such

as eosinophils in our data. One might imagine a more significant contribution to the precancerous milieu from the neutrophilic inflammation than the eosinophilic.
CD8+ T-cells are more dominant than CD4+ T-cells, in mild to moderate COPD compared to in subjects without COPD, which might be related to the susceptibility of viral infections (205). One study found an increased expression of programmed cell death (PD)-1 in CD8+ T cells and the ligand PD-L1 in patients with mild to moderate COPD (206). Cell cycle arrest is caused by the interaction between PD-1 and PD-L1, which results in T-cell anergy, meaning a reduced reaction to foreign substances by the body's defense mechanisms. External administration of the influenza virus led to an increased tendency of dysfunctional CD8+ T cells (206). Increased expression of PD-1 on CD8+ T-cells was also found to be higher in peripheral blood of patients with NSCLC, and their interaction with PD-L1 in the tumor milieu is now an established target for antibody-based therapeutic interventions such as pembrolizumab in advanced stages of cancer (207, 208). The increased expression of PD-1 on CD8+ T-cells might represent a link between lung cancer and COPD, and to AECOPD induced by airway virus.

Third, viruses and bacteria generate most AECOPD (26, 27). Several carcinogenic viruses and bacteria have been identified. (209, 210). Whether some virus or bacteria might cause cancer development in the lungs as well, remains unknown. Influenza increases the risk of lung cancer in some studies (211, 212). One large population-based cohort study from Taiwan found a decreased risk of lung cancer in COPD patients with influenza vaccination (212). They were able to show a dose-dependent effect and hypothesized less frequent exacerbations due to influenza with the vaccine, thus reducing persistent inflammation. They also suggested the trigger of immune response and antitumor defense with the vaccines (212). This study did, however, not have information on tobacco exposure. Studies that can adjust for smoking are needed to confirm their findings. Whether the mechanisms linking influenza to increased risk of lung cancer, also apply to other airway bacteria or viruses, such as SARS-CoV-2, remains unknown. Studies on different triggers of AECOPD and lung cancer might help answer some of these questions. It could be that the exacerbations in COPD patients

with and without coexisting asthma mainly have different triggers, and therefore represent a different risk of lung cancer.

Fourth, several studies have found a protective effect on lung cancer risk with inhaled corticosteroids (ICS) (54, 213-215). This could be due to reduced airway inflammation and decreased cell turnover, which lowers the risk of propagation of genetic errors (216). The protective effect of ICS on lung cancer in COPD patients might also be caused by reduced EMT (217). According to one report, ICS might have the ability to improve airway EMT in COPD (218). Characteristics of EMT are seen in the airways of smokers and COPD patients. Since NSCLC cells might achieve EMT phenotype (219), EMT has been suggested as a possible connection between cancer and COPD (220). Patients with coexisting asthma might have used more inhaled steroids, which might explain why AECOPD increases the risk of lung cancer only in COPD patients without asthma in our cohort.

Fifth, tobacco exposure is a considerable risk factor for COPD and lung cancer. In our cohort, the COPD patients with asthma smoked less than those without asthma. The effect of smoking on chronic inflammation and enzymatic imbalance might be less broad in asthma patients. A recent report showed that the acute effects of cigarette smoke and associated infection play an essential role in driving complete EMT. The extra insult caused by an infection can amplify EMT, causing chronically remodeled airways, as seen in COPD (221).

6.4. Lung cancer screening in a COPD population

Even though we were able to confirm that both the COPD-LUCSS and the NLST selection criteria were associated with an increased risk of lung cancer, the AUC-values were 0.61 and 0.59, respectively, indicating poor discriminatory abilities for both scores (222). Almost half, 30% and 50%, of the lung cancers occurred in the low risk groups (Table E3, Paper III), suggesting that neither scores in their current form should be used to select individuals for lung cancer screening in a population of COPD patients. De

Torres et al. (76) stated that the COPD-LUCSS was better than the NLST selection criteria at predicting lung cancer. This was examined by a visual comparison of Kaplan-Meier curves and not tested by an objective statistical test. In our cohort, we found no statistically significant differences between the COPD-LUCSS and the NLST selection criteria (Paper III).

The National Comprehensive Cancer Network recommends lung cancer screening for people who fulfill criteria similar to the NLST selection criteria (6). In Europe, there is no nationwide lung cancer screening to this date. The NELSON trial, a large Dutch-Belgian trial including 7 900 subjects in the CT screening arm and 7 892 in the control arm recently reported significantly lower lung cancer mortality among participants who underwent CT screening compared to no screening (70). Trials are ongoing in other European countries (223, 224), and lung cancer screening is being discussed in most countries, including in Norway and other Nordic countries (225).

There are still several unsolved issues concerning lung cancer screening. We do not know the optimal screening frequency, the necessary duration of screening, the optimal target population, how to define criteria for a "positive" finding, how to identify diagnostic follow-up protocols to minimize evaluations of false-positive findings, how to get sufficiently trained radiologists, a plan to reduce overdiagnosis or a plan for incidental findings (226). The European Respiratory Society and the European Society of Radiology recommend that the European countries work collectively to find the best solution for the implementation of lung cancer screening (226).

Even though COPD is a known risk factor for lung cancer risk (36), most randomized control trials recruited participants based on age and smoking history alone (62, 64-68). All three papers in this thesis confirm an increased risk of lung cancer in subjects with COPD, which suggests that COPD should be considered when evaluating a target population for screening. A recently published study by Park et al. found that COPD in never-smokers was a stronger predictor of lung cancer than smokers without COPD (159). Even though the COPD-LUCSS turned out to have poor discriminatory abilities

in our cohort, emphysema remains a strong predictor for lung cancer. Severe COPD is associated with poor outcome in lung cancer (227). Thus, some patients with severe COPD might benefit from early detection of lung cancer. Which patients suffering from COPD would make the best target population, and whether patients with particular features of COPD could benefit more from lung cancer screening than others, needs more investigation.

7. Conclusions

Paper I

Emphysema assessed quantitatively on CT was an independent risk factor for both non-pulmonary cancer and lung cancer. Airway wall thickness in terms of Pi10 did not predict non-pulmonary cancer or lung cancer.

Paper II

AECOPD was significantly associated with an increased risk of lung cancer only in COPD patients without coexisting asthma. There was a significant difference between the effect of AECOPD on lung cancer based on coexisting asthma.

Paper III

The COPD-LUCSS and the NLST criteria were associated with increased risk of lung cancer. The AUC values showed that both scores have poor discriminatory abilities in our cohort. COPD-LUCSS was not significantly better than the NLST criteria in our cohort of COPD patients.

8. Suggestions for future research

The findings of this thesis give the basis for several future research questions:

- CT technology keeps improving and has become a more significant part of diagnostics in COPD patients. The lack of standards for quantification of emphysema remains a problem for comparison of results in different studies. The lack of a reference group is also a problem for evaluation of the risk of future disease. Studies addressing these issues should be generated.
- In our cohort, we had validated histological types of lung cancer, but not sufficient lung cancer cases to examine predictors and histological types of lung cancer properly. Studies on emphysema and AECOPD and types of lung cancer should be conducted.
- Studies with sufficient statistical power to look into emphysema and the risk of different cancer types outside the lungs are needed.
- The validity of retrospective risk factors, such as AECOPD and asthma in our case, is a universal problem. Other studies with validated exacerbations and asthma diagnosis are needed to confirm our findings.
- Studies on types of exacerbations, including inflammatory markers, such as eosinophils and risk of lung cancer, are needed to understand more of the mechanisms linking the two diseases.
- Studies on seasonal AECOPD, including patients from different areas of the world, could be beneficial to study viruses' impact on lung cancer. Virus exposure varies geographically and with season.
- One study found that influenza vaccination in COPD patients was protective against lung cancer. This study lacked information on significant confounders. More studies should be conducted to confirm this finding.
- SARS-CoV-2 is attacking the world, also generating much data on virus status. These data could generate baseline data for prospective cohorts to examine its effect on future lung cancer.

- Patients suffering from COPD caused by other risk factors such as biomass fuel or outdoor air pollution might represent different phenotypes of COPD, whether they have a different risk of lung cancer remains unknown. Studies examining this link should be done.
- It remains unknown whom to target for lung cancer screening. RCTs with COPD or emphysema as inclusion criteria could help to find those who would benefit the most.

9. Errata

Methods section of Paper I and Paper III

The use of a slice thickness of 1.0 mm at 20 mm intervals when acquiring the CT images, was specified for the GenKOLS study. The slice thickness used was, however, 1.25 mm at 20 mm intervals. This error was only in the description, and the correct slice thickness was used for all CT analyses. Thus, this had no consequences for the data presented in the two papers.

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APPENDICES

Appendix A

Invitation, information and consent letter sent to previous participants in SOHAS (Norwegian version and English translation).
Details regarding the letters sent to subjects from HCRHS and the HUH COPD patient registry follows immediately after the SOHAS letter.

(Norwegian version)

Universitetet i Bergen, Lungeavdelingen, Institutt for Indremedisin, N-5021 Haukeland Sykehus
Bergen <dato>

DELTAKERINFORMASJON OG SAMTYKKESKJEMA I ETTERUNDERSØKELSE AV ASTMA OG ASTMALIGNENDE SYKDOMMER (KOLS) I BERGEN OG OMEGN I 2002-2004

Kjære <navn>!

Takk for din interesse. Astma og astmalignende sykdommer øker kraftig i Norge og i verden for øvrig. Vi prøver nå å finne årsaken til astmalignende sykdommer (emfysem, KOLS). Hvorfor får noen slike sykdommer av å røyke, mens andre ikke får det? Vi gjennomfører en undersøkelse ved Universitetet i Bergen og Haukeland sykehus i samarbeid og med finansiell støtte fra et legemiddelfirma (GlaxoSmithKline) som ønsker å utvikle nye legemidler mot sykdommen og nye metoder for å påvise sykdommen på et tidlig stadium. I alt vil ca. 5500 personer fra Bergen og omegn bli invitert til å delta.

** Du deltok i vår undersøkelse omkring astma og allergi i 1998/1999. Vi vil takke deg for det. Din deltagelse har gitt oss verdifull kunnskap om kroniske lungesykdommer. Vi håper du igjen kan hjelpe oss.*

Vi ber deg om å fylle ut vedlagte spørreskjema og tar det med til helseundersøkelsen den … 200… klokken…. som vi avtalte i telefonen. Instruksjon for utfylling står øverst på spørreskjemaet. Dersom det nevnte tidspunktet ikke skulle passe, vennligst gi beskjed mellom klokken 08.00-11.00, telefon… …eller epost… …

Ved undersøkelsen på sykehuset måler vi din lungefunksjon med en pustetest (spirometri). Evnen til å utvide luftveiene vil vi ved helseundersøkelsen teste med et legemiddel som heter salbutamol (Ventoline) som skal pustes inn. Det anvendes daglig av mange astmatikere i Norge. De fleste merker ikke noe ved å puste inn salbutamol. Noen kan få lett hjertebank og lett fingerskjelving. Mindre vanlig er hodepine og munn-/halsirritasjon. Vi undersøkte i 1996-99 ca. 6000 personer med denne testen og opplevde ingen bivirkninger. Denne for-undersøkelsen tar ca. en halv til en time.

Avhengig av hva denne puste-testen viser vil du bli invitert til å delta i videre undersøkelser. Du vil da få ytterligere informasjon, og kan velge om du vil være med eller ikke. Hvis du vil være med, vil vi gjøre noen flere enkle lungefunksjonsundersøkelser. En del av dere vil også få tilbud om røntgenfotografering. Vi vil da se på om arvemateriale og eggehvitestoffer i blod og urin kan ha noe med astmalignende sykdommer (KOLS) å gjøre. Dersom du blir med i denne videre undersøkelsen, vil det totalt kunne ta opp til to timer (inklusive forundersøkelsen).

Deltagelsen i både for-undersøkelsen og den videre undersøkelsen er frivillig. Du vil ikke bli behandlet annerledes av oss hvis du ikke ønsker å gjøre pusteprøven eller noen andre prøver. Du forplikter deg ikke til å delta i den videre undersøkelsen selv om pusteprøven skulle tilsi det.

Undersøkelsen er gratis. Vi betaler parkeringsutgifter på sykehuset, og andre transportutgifter. Undersøkelsen er ikke ment å gi deg en helsegevinst. Du vil få skriftlig tilbakemelding om resultatet av lungefunksjonsmålingen, uansett resultat

(Fortsetter…)

(English translation)
University of Bergen, Pulmonary Section, Institute of Medicine, N-5021 Haukeland Sykehus
Bergen <date>

PARTICIPANT INFORMATION AND CONSENT FORM: POST-INVESTIGATION OF ASTHMA AND ASTHMA-LIKE DISEASE (COPD) IN BERGEN IN 2002-2004

Dear <name>!

Thank you for your interest. Asthma and asthma-like disease increases dramatically in Norway and in the world in general. We are now trying to find the cause of asthma-like diseases (emphysema, COPD). Why do some people develop these diseases due to smoking, while others don't? We conduct a survey at University of Bergen and Haukeland University Hospital in collaboration with and with financial support from a pharmaceutical company (GlaxoSmithKline) who wish to develop new drugs against the disease and new methods for detecting the disease at an early stage. In total, approx. 5500 people from Bergen and the surrounding communities will be invited to participate.

** You participated in our survey about asthma and allergies in 1998/1999. We want to thank you for that. Your participation has given us valuable knowledge about chronic lung diseases. We hope you can help us again.*

We ask you to fill out the enclosed questionnaire and bring it to the medical examination on ... 200 ... at .... as we agreed on the phone. Instructions for filling out the questionnaire are given at the top. If the agreed time is not convenient, please let us know by phone … (8:00 to 11:00 a.m.) or by email ...

During the survey at the hospital we will measure your lung function using a breathing test (spirometry). Your ability to expand the airways will also be tested during the health survey, using a inhaled medicine called salbutamol (Ventoline). It is used daily by many asthmatics in Norway. Most people do not experience any side effects when inhaling salbutamol, but some can feel palpitations and light hand tremor. Less common are headaches and irritation in the mouth and throat. In 1996-99 we examined approx. 6000 people using this test, and experienced no side effects. This first part of the survey will take approx. one half to one hour.

Depending on the result of breathing test, you may be invited to participate in further investigations. You will then get further information and can choose whether to participate or not. If you want to join, we will do some more simple pulmonary function tests. Some of you will also be offered X-ray photography. We will then look at whether genes and proteins in blood and urine may be related to asthma-like disease (COPD). If you join this extended part of the examination, the total could take up to two hours (including the first part of the examination).

Participation in both the first part and the extended part of the survey is voluntary. You will not be treated differently by us if you do not want to take the breathing test or any other samples. You are not committed to participate in the extended investigation even though the breathing test should indicate that.

The survey is free. We cover parking expenses at the hospital, and other transportation costs.
The survey is not intended to provide you any health benefit. You will receive written feedback on the results of lung function tests, regardless of the outcome.

(Continues…)

(…fortsatt fra forrige side)

Selv om du velger å delta, kan du fritt trekke deg på et hvilket som helst tidspunkt og bli fjernet fra videre oppfølging. Alle deltakere i denne undersøkelsen er forsikret etter de samme regler som gjelder for pasienter som blir undersøkt og behandlet på Haukeland sykehus. Dersom resultatene av undersøkelsene ved dette studiet indikerer at du skulle trenge videre undersøkelse eller behandling så vil dette bli dekket av vanlige offentlige forsikringssystemer i Norge. Det er GlaxoSmithKline og Lungeseksjonen, Universitetet i Bergen og deres samarbeidspartnere som eier studien og som kan bruke informasjonen for utvikling av legemidler eller annen informasjon som kan produsere økonomiske fordeler for institusjonene. Resultatene av studiene kan være vitenskapelige oppdagelser og både GlaxoSmithKline og andre forskere kan søke om patenter for slike oppdagelser. Vi gjør oppmerksom på at kontrollmyndighetene vil kunne ha behov for a sjekke at opplysninger gitt i undersøkelsen stemmer med opplysninger i din sykehusjournal for å studere undersøkelsens kvalitet.

Undersøkelsen er godkjent av den Regionale Etisk Komite for Helseregion Vest, og Datatilsynet. Alle opplysninger vil bli behandlet fortrolig. De som arbeider med prosjektet har taushetsplikt både som forskere og helsepersonell. Vi vil gjerne beholde opplysningene med tanke på senere oppfølgingsundersøkelser. Skulle du ha noen spørsmål om prosjektet eller spørreskjemaet, ta gjerne kontakt på telefon: … … … eller … … … ...

Med vennlig hilsen

Amund Gulsvik Prosjektansvarlig Professor, overlege Universitetet i Bergen og Lungeavdelingen, Haukeland sykehus	Per Bakke Overlege, professor II, Lungeavdelingen, Haukeland sykehus og Universitetet i Bergen	Jan Brøgger Lege, universitetsstipendiat Universitetet i Bergen

Jeg har lest informasjonen og er villig til å delta i forundersøkelsen og pustetesten. Jeg er klar over at jeg kan trekke meg når som helst uten å oppgi grunn.

Dato … … … … … Underskrift … … … …

(…continued from previous page)

Even if you choose to participate, you may withdraw at any time and be removed from further investigation. All participants in this study are insured by the same rules that apply to patients that are examined and treated at Haukeland Hospital. If the results of investigations of this study indicate that you would need further examination or treatment, this will be covered by regular public insurance systems in Norway. GlaxoSmithKline and the Pulmonary Section, University of Bergen and their partners own this study and may use the information for the development of drugs or other information that may produce economic benefits for the institutions. The results of the studies may be scientific discoveries and both GlaxoSmithKline and other researchers can apply for patents for such discoveries. We note that the supervisory board may need to check that the information given in the survey matches the information in your hospital records to study the quality of the survey.

The survey was approved by the Regional Ethics Committee for Health Region West, and the Data Inspectorate. All information will be treated confidentially. Those working on the project have confidentiality both as researchers and health professionals. We would like to keep the information we have gathered to fascilitate later follow-up investigations. Should you have any questions about the project or the questionnaire, please contact us by phone: ... ... or ... ...

Sincerely,

Amund Gulsvik
Project Manager
Professor, Consultant
University of Bergen and
Pulmonary Dept, Haukeland
University Hospital

Per Bakke
Consultant, Professor
Pulmonary Dept., Haukeland
University Hospital and
University of Bergen

Jan Brøgger
MD, Research Fellow
University of Bergen

I have read the information and I am willing to participate in the first part of this study and to take a breathing test. I am aware that I can withdraw at any time without giving any reason.

Date ... ... Signature ... ...

* The above information, invitation and consent letter was sent to previous participants in SOHAS. Almost identical letters were also sent to previous participants in HCRHS and to participants that were selected from the HUH COPD patient registry. These letters differed from the above letter only by one paragraph, the second, which is marked with an asterix and written in *italics*. This paragraph describes the background for why the participants were invited. Below, you will find the alternative second paragraphs used in the letters that were sent to the participants originating from the HUH COPD registry and HCRHS, respectively, in Norwegian and English versions:

HUH COPD registry (Norwegian)
Vi har tatt kontakt med deg, fordi du har vært ved vår poliklinikk eller har vært innlagt pga. astma eller astmalignende sykdom (KOLS), ved Lungeavdelingen, Haukeland sykehus.

HUH COPD registry (English translation)
We have contacted you because you have been at our outpatient clinic or have been hospitalized due to asthma or asthma-like disease (COPD), at the pulmonary department at Haukeland University Hospital.

HCRHS (Norwegian)
Du deltok i vår undersøkelse omkring astma, allergi og andre lungesykdommer i 1985. Vi vil takke deg for det. Din deltagelse har gitt oss verdifull kunnskap om kroniske lungesykdommer. I 1986-87 møtte nærmere halvparten av dere til en legeundersøkelse ved Haukeland sykehus og i 1996-97 ble dere alle invitert til en ny helseundersøkelse ved Haukeland sykehus. Vi ønsker nå å gjenta denne helseundersøkelsen for å kartlegge din helsetilstand og hvordan din pusteevne har forandret seg.

HCRHS (English translation)
You participated in our survey about asthma, allergies and other respiratory diseases in 1985. We want to thank you for that. Your participation has given us valuable knowledge about chronic lung diseases. In 1986-87 some of you (approx. 50%)

attended a medical examination at the Haukeland hospital, and in 1996-97 you were all invited to a new medical examination at Haukeland Hospital. We now wish to repeat this health survey to determine your current health condition and to see how your lung function has changed.

Appendix B

Postal questionnaire (Norwegian version and English translation)

(Norwegian version)

Universitetet i Bergen, Lungeavdelingen, Institutt for Indremedisin N-5021 Haukeland Sykehus

SPØRRESKJEMA FOR
ETTERUNDERSØKELSE AV ASTMA OG ASTMALIGNENDE SYKDOMMER (KOLS) I BERGEN OG OMEGN I 2002-2004

Hvis du ikke kan gi et helt nøyaktig svar, så fyll ut etter beste skjønn. Hvis det er spørsmål du ikke kan svare på, så la det stå åpent. Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller svart farge ved utfylling. Det er viktig at du går frem slik:

- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall

Eksempel: avkrysning slik: ☒ ikke slik: ☒

tall: | 1 | 2 | 3 |

A. Plager fra luftveiene

1. Hoster, harker eller kremter du vanligvis om morgenen?
2. Hoster du vanligvis ellers om dagen?
3. Har du vanligvis oppspytt når du hoster eller harker?
4. Hoster du daglig til sammen 3 måneder eller lenger i løpet av et år?
5. Har du i løpet av de siste par årene i forbindelse med forkjølelse hatt hoste og/-eller oppspytt som har vart i mer enn 3 uker?
6. Blir du mer tungpustet (andpusten) enn jevnaldrende når du går i motbakker?
7. Blir du tungpustet når du går opp 2 etasjer i vanlig fart?
8. Blir du tungpustet når du går med vanlig fart på flat mark?
9. Er du tungpustet når du sitter i ro?
10. Hender det at du har anfall av tung pust?
11. Har du noen gang piping (pipelyd) i brystet?
12. Har du noen gang i løpet av de siste 12 månedene hatt pipelyder (piping) i brystet? (Med pipelyder menes høye eller dype lyder som også kan være svake)

Hvis ja:

13. Har du vært tungpustet i forbindelse med at du hadde pipelyder i brystet?
14. Har du hatt slike pipelyder når du ikke har vært forkjølet?

B. Allergier

1. Har du noen gang hatt høysnue?
2. Hvis ja:
   Har du de siste 12 måneder hatt høysnue?
3. Har du noen gang hatt høysnue og/eller pollenallergi?

C. Astma eller astmaliknende sykdom (KOLS) i familien

1. Har følgende av dine biologiske slektninger hatt astma eller astmaliknende sykdommer (KOLS, emfysem)?

a) Mor:
b) Far:

(Fortsetter…)

(English translation)

University of Bergen, Pulmonary Section, Institute of Medicine, N-5021 Haukeland Sykehus

QUESTIONNAIRE FOR
POST-INVESTIGATION OF ASTHMA OG ASTHMA-LIKE DISEASE (COPD) IN BERGEN AND SURROUNDING COMMUNITIES IN 2002-2004

If you cannot give an exact answer, please fill out at your best discretion. If there are questions you cannot answer, leave it blank. The completed form will be read by a machine. Use blue or black color when filling it out. It is important that you proceed as follows:

- in the small boxes, please tick the answer that best suits you
- in the large boxes, please type numbers

Example: Tick like this: ☒ not like this: ☒

numbers: | 1 | 2 | 3 |

A. Symptoms from the respiratory tract

1. Do you usually cough, hark or hawk in the morning?
2. Do you usually cough during the rest of the day?
3. Do you usually have phlegm when you cough or hark?
4. Do you cough daily for 3 or more months in one year?
5. Have you, in the last couple of years, had cough and / or phlegm for more than 3 weeks in conjunction with a cold?
6. Do you experience more shortness of breath than your peers when walking uphill?
7. Do you get breathless when ascending two flights of stairs at normal speed?
8. Do you get breathless when walking at normal speed on level ground?
9. Do you get breathless when sitting quietly?
10. Do you have attacks of breathlessness?
11. Have you ever experienced wheezing in your chest?
12. Have you experienced wheezing in your chest in the last 12 months? (Wheezing is high- or low-pitched sounds that can also be weak.)

If yes:

13. Do you get breathless in conjunction with the wheezing?
14. Have you experienced wheezing when you were not having a cold?

B. Allergies

1. Have you ever had hay fever?
2. If yes:
   Have you had hay fever in the last 12 months?
3. Have you ever had hay fever and / or pollen allergy?

C. Asthma or astma-like disease (COPD) in the family

1. Have any of your biological relatives had asthma or asthma-like disease? (COPD, emphysema)?

a) Mother:
b) Father:

(Continues…)

(…fortsatt fra forrige side)

D. Lunge- og hjertesykdommer

Er du noen gang blitt behandlet av lege eller har du vært innlagt i sykehus for en av de sykdommene som er nevnt nedenfor?

1. Astma?
   - Hvis ja:
   - Hvor gammel var du da sykdommen begynte?
   - Hvis du ikke lenger har astma, hvor gammel var du da den da seg?
2. Bronkitt?
   - Hvis ja:
   - Hvor gammel var du da sykdommen begynte?
   - Hvis du ikke lenger har bronkitt, hvor gammel var du da den ga seg?
3. Emfysem?
   - Hvis ja:
   - Hvor gammel var du da sykdommen begynte?
4. Kronisk obstruktiv lungesykdom (KOLS)?
   - Hvis ja:
   - Hvor gammel var du da sykdommen begynte?
5. Hjerteinfarkt?
6. Angina pectoris?

E. Røykevaner

1. Røyker du daglig for tiden?

Hvis ja:

2. Røyker du sigaretter daglig (håndrullede eller fabrikkfremstilte)?

Hvis nei:

3. Har du røykt sigaretter daglig tidligere?

Hvis ja:

4. Hvor lenge er det siden du sluttet?
   - Mindre enn tre måneder
   - Tre måneder til ett år
   - Ett år til fem år
   - Mere enn fem år

Følgende spørsmål besvares *kun* hvis du røyker nå eller har røykt tidligere:

6. Hvor mange år har du røykt daglig? ___
7. Hvor mange sigaretter røyker du eller røykte du daglig? (oppgi antall pr dag, både håndrullede og fabrikkfremstilte) _____
8. Hvis du røyker, har noen lege anbefalt deg å slutte å røyke?
9. Har du prøvd nikotinplaster, nikotintyggegummi eller nikotininhalator for å slutte å røyke?
10. Har du prøvd røykesluttpillen Zyban for å slutte å røyke?
11. Har du deltatt på røykeavvenningsmøter eller kurs?

F. Din utdannelse og arbeid

1. Vennligst kryss av for det utdanningsalternativ som passer best for deg:

Tidligere folkeskole eller nåværende 9-årig grunnskole
Framhaldsskole, folkehøyskole og andre tilsvarende skoler
Middelskole, realskole, gymnas, videregående skole, yrkesskole eller annen fagskole
Høyskole, universitet

2. Har du noen gang hatt en arbeidsplass med mye støv eller gasser i luften?

(Fortsetter…)
(…continued from previous page)

D. Lung and heart disease

Have you ever been treated by a physician or admitted to a hospital because of any of the below mentioned diseases?

1. Asthma?
   - If yes:
   - How old were you when the disease started?
   - If you no longer have asthma, how old were you when the symptoms stopped?
2. Bronchitis?
   - If yes:
   - How old were you when the disease started?
   - If you no longer have bronchitis, how old were you when the symptoms stopped?
3. Emphysema?
   - If yes:
   - How old were you when the disease started?
4. Chronic obstructive lung disease (COPD)?
   - If yes:
   - How old were you when the disease started?
5. Heart attack?
6. Angina pectoris?

E. Smoking habits

1. Are you currently a daily smoker?

If yes:

2. Do you smoke cigarettes daily (hand-rolled eller prefabricated)?

If no:

3. Have you previously been a daily smoker?
   If yes:
4. How long is it since you quit?
   - Less than 3 months
   - 3 months to a year
   - 1 to 5 years
   - More than 5 years

The following questions should only be answered if you are a current or previous smoker:

6. For how many years have you been a daily smoker? ___
7. How many cigarettes do you or did you smoke per day (both hand-rolled and prefabricated)? _____
8. If you are a current smoker, has a physician ever advised you to quit smoking?
9. Have you tried nicotine patches, gum or inhaler in order to quit smoking?
10. Have you tried to quit smoking using the quitting-pill Zyban?
11. Have you participated on any smoke quitting sessions or meetings?

F. Your education and work

1. Please tick the option that best describes your educational level:

Former primary school or present 9-year primary school
Continuation school, 1-year people's college and similar schools
Lower/upper secondary school or technical school
College or university

2. Have you ever had a work-place with much dust or fumes in the air?

(Continues…)

(…fortsatt fra forrige side)

G. Mors og fars utdannelse

1. Vennligst kryss av for det utdanningsalternativ som passer best for din mor og far:

	FAR	MOR
Tidligere folkeskole eller nåværende 9-årig grunnskole		
Framhaldsskole, folkehøyskole og andre tilsvarende skoler		
Middelskole, realskole, gymnas, videregående skole, yrkesskole eller annen fagskole		
Høyskole, universitet		
Vet ikke		

H. BRUK AV HELSETJENESTER OG TRYGD

1. Har du astma, bronkitt emfysem eller kronisk obstruktiv lungesykdom?
Hvis nei, hopp til neste seksjon.
Hvis ja:
    2. Bruker du astmamedisiner nå? (inkludert spray, pulverinhalasjoner, tabletter)
    3. Går du til kontroll hos lege for den sykdommen?
    Hvis ja:
        4. Går du til:
            Allmenpraktiker, kommunelege
            Bedriftslege
            Lungelege eller spesialist i lungesykdommer
            Annen lege
        Når var du til kontroll sist? for __ måneder siden
    Hvor mange ganger har du vært innlagt på sykehus for den sykdommen siste 12 måneder?
    __ ganger
    Er du i lønnet arbeid?
    Hvis ja:
        Hvor lenge har du vært sykemeldt tilsammen pga. den sykdommen siste 12 måneder
            Ingen dager
            0-7 dager (En uke eller mindre)
            8-30 dager (Mere enn en uke, men ikke mere enn en måned)
            31-90 dager (Mere enn en måned, men ikke mere enn tre måneder)
            Over 90 dager (Mere enn tre måneder)
    Er du uføretrygdet pga. overnevnte sykdommer?

I. Høyde og vekt

1. Hvor høy er du (cm)?
2. Hvor mye veier du (kg)?

Takk for at du har tatt deg tid til å fylle ut skjemaet! Husk å ta det med til avtalt helseundersøkelse på Haukeland sykehus.

(…continued from previous page)

G. Parents' education

1. Please tick the option that best describes your parents' educational level:

	FATHER	MOTHER
Former primary school or present 9-year primary school		
Continuation school, 1-year people's college and similar schools		
Lower/upper secondary school or technical school		
College or university		
Don't know		

H. USE OF HEALTH SERVICES AND SOCIAL SECURITY

1. Do you have asthma, bronchitis, emphysema or chronic obstructive pulmonary disease?
If no, skip to the next section.
If yes:
    2. Are you currently using asthma medication? (Included spray, dry powder inhalers and pills)
    3. Are you seeing a physician for the above mentioned diseases?
    If yes:
        4. Are you seeing a:
            General practitioner
            Company doctor
            Pulmonary specialist
            Other physician
        When did you last see your physician? __ months ago
    How many times have you been admitted to a hospital for the above mentioned diseases in the last 12 months? __ times
    Are you employed?
    If yes:
        What is the total number of days that you have been on sick-leave due to the above mentioned diseases in the last 12 months?
            No days
            0-7 days (One week or less)
            8-30 days (More than a week, but less than a month)
            31-90 days (More than a month, but less than 3 months)
            More than 90 days (More than 3 months)
    Are you receiving disability pension due to the above mentioned diseases?

I. Height and weight

1. How tall are you (cm)?
2. How much do you weigh (kg)?

Thank you for taking the time to fill out this form! Please remember to bring the form when you attend the scheduled medical examination on Haukeland University Hospital.

Appendix C

Information and consent form, part II (Norwegian version and English translation)

(Norwegian version)

Universitetet i Bergen, Lungeavdelingen, Institutt for Indremedisin N-5021 Haukeland Sykehus

Deltakerinformasjon/samtykkeskjema II

Forespørsel om deltagelse i en undersøkelse på arvemateriale hos pasienter med astmalignende sykdom (kronisk obstruktiv lungesykdom, KOLS) og kontrollpersoner (PROTOKOLL GenKOLS)

Du er blitt forespurt om å delta i en studie som gjøres av Universitetet i Bergen i samarbeid med og med finansiell støtte av legemiddelfirmaet GlaxoSmithKline (GSK). Før du bestemmer deg for å delta, bør du sette deg inn i hva studien går ut på. Denne informasjonen forklarer studien slik at du får grunnlag til å vurdere om du vil delta eller ikke. Studien er tilrådd av Regional Komite for medisinsk forskningsetikk, Helseregion Vest (REK III).

Hensikten
Hovedhensikten med studien er å undersøke arvematerialer (DNA og RNA som inneholder gener) og proteiner (lages med informasjon fra gener) som har noe med KOLS å gjøre. Du er spurt om du vil være med i denne undersøkelsen enten fordi du har astmaliknende sykdom (KOLS), eller fordi du er røyker eller er tidligere røyker men ikke lider av astmaliknende sykdom (KOLS).

Ved å sammenligne ditt arvematerialer og visse proteiner som lages i deg, med arvematerialer og proteiner som lages i personer som ikke har KOLS, kan vi få nyttig informasjon om hva gener har å si for denne sykdommen. Universitetet i Bergen og GSK har satt i gang denne studien, og de betaler kostnadene for studien. Til denne studien trenger vi resultater fra omlag 2000 deltagere. Studien gjøres i Norge av professor overlege Amund Gulsvik, som er spesialist på lungesykdommer, og hans medarbeidere.

Hva som forventes av deg dersom du bestemmer deg for å delta
Før studien kan starte må du lese denne informasjonen og du vil også få anledning til å stille spørsmål om det er noe du lurer på. Det blir også spurt etter din families sykehistorie og etnisk tilhørighet.
Du må gi skriftlig samtykke for å få delta.

Hva blir jeg bedt om å gjøre hvis jeg samtykker til å delta?
Du vil bli bedt om å gi informasjon om din sykdom og om din generelle helsetilstand og om evt medisiner du tar. Du har allerede fått gjennomført en pusteprøve (spirometri) med astmamedisinen Ventoline og lytting på lungene med stetoskop. Den andre testen (Gas Transfer) måler dine lungers kapasitet til å utveksle gasser, med en ufarlig testgass, som er hovedfunksjonen til lungene.

Dersom du ikke har hatt utført en CT undersøkelse (en type røntgenundersøkelse av lungene) i løpet av de siste 2 år er det mulig at dette gjøres i forbindelse med denne studien. Testen krever at du må puste helt ut og puste dypt inn – for så å holde pusten opp til 10 sekunder – før du puster godt ut igjen.
Det vil bli tatt blodprøve av deg. Denne vil bli brukt for undersøkelse av ditt arvemateriale (DNA) og andre blodprodukter, for eksempel proteiner. Det vil bli tatt ca. 60 ml (tilsvarer 5 ss) blod.

Kriterier for deltagelse
Du må være 40 år eller eldre, og enten ha diagnosen KOLS og en sykehistorie som passer med studieplanen, eller være røyker eller tidligere røyker og fri for KOLS og ellers passe med studieplanen.

Mulig risiko ved å delta
Undersøkelsene som inngår i denne studien gjøres slik de blir gjort vanligvis på sykehuset. Noen synes det er ubehagelig / vondt å få tatt blodprøve. Faren for infeksjon er liten. Testgassen er ufarlig.

(Fortsetter…)

(English translation)

University of Bergen, Pulmonary Section, Institute of Medicine, N-5021 Haukeland Sykehus

Participant information/consent form II

Request for participation in a survey of genes in patients with asthma-like disease (chronic obstructive pulmonary disease, COPD) and control subjects (PROTOCOL GenKOLS)

You have been asked to participate in a study carried out by the University of Bergen in cooperation with and with financial support from the pharmaceutical company GlaxoSmithKline (GSK). Before you decide to participate, you should familiarize yourself with what the study entails. This information explains the study to give you a basis to decide whether or not to participate. The study is recommended by the Regional Ethical Committee for Medical Research, Health Region West (REK III).

The purpose
The main purpose of this study is to investigate the genetic material (DNA and RNA that contains genes) and proteins (made with information from genes) that are related to COPD. You have been asked to participate in this study either because you have asthma-like disease (COPD), or because you are a smoker or former smoker but not suffering from asthma-like disease (COPD).

By comparing your genetic material and certain proteins that are produced within you, with genetic material and proteins from people with COPD, we can get useful information about the influence of genes on this disease. The University of Bergen and GSK has initiated this study, and they finance the costs of this study. For this study we need results from approx. 2000 participants. The study is carried out in Norway by professor and pulmonary consultant Amund Gulsvik and his co-workers.

What is expected of you if you decide to participate
Before the study can begin, you must read this information, and you will also have the opportunity to ask questions. You will also be asked about your family's medical history and ethnicity.
You must give written consent to participate.

What will I be asked to do if I agree to participate?
You will be asked to provide information about your diseases and your general health, and about any medication you might be taking. You have already completed a breathing test (spirometry) with the asthma medication Ventoline, and we have listened to your lungs with a stethoscope. The second test (Gas Transfer) measures the capacity of your lungs to exchange gases using a harmless test gas, and this is the main function of the lungs.

If you have not undergone a CT examination (a type of X-ray examination of the lungs) within the last 2 years, it is possible that this will be done in connection with this study. The test requires you to exhale completely and inhale deeply - and then hold your breath for up to 10 seconds - before you can exhale.
Blood samples will be taken. These will be used for analyses of your genetic material (DNA) and other blood components such as proteins. Approx. 60 ml (equivalent to 5 tablespoons) of blood will be drawn.

Criteria for participation
You must be 40 years or older. You must either have diagnosed COPD and a medical history that fits the study protocol, or be a current or former smoker without COPD and otherwise fit the study protocol.

Possible risks of participating
The tests and examinations included in this study are performed the way they are usually done at the hospital. Some think it is unpleasant / painful to have blood tests taken. The risk of infection is small. The test gas is harmless.

(Continues…)

(…fortsatt fra forrige side)

Hvis en CT undersøkelse blir utført vil du få en mindre strålingsdose, som når man flyr fra Norge til USA. Jo mere stråling du får i løpet av ditt liv, jo større er risikoen for kreft og svulster eller for å påføre forandringer til dine gener. Hvis du har mistanke om at du er gravid skal du unngå å ta denne testen.

Mulige fordeler ved å delta
Du vil ikke ha noen direkte nytte av å delta i en slik studie. Resultatene fra denne studien kan bli nyttig for pasienter med KOLS i fremtiden. Vi kan lære mer om sykdommen KOLS og vi kan få informasjon som kan gjøre det mulig å utvikle bedre medisin for pasienter med KOLS.
Resultatene vil ikke være klare før om flere år. Informasjon fra lungefunksjonstesten vil bli gitt deg skriftlig av en lege. Du vil også bli informert om resultatene av røntgenbildet av lungene, hvis dette blir tatt.

Personlige opplysninger og konfidensialitet
Alle person-opplysninger behandles konfidensielt og i henhold til kravene i de nye forskriftene til Personregisterloven. Blodprøven og de medisinske opplysningene identifiseres med et studieidentitetsnummer, ikke navnet eller personnummeret ditt. Det er kun prosjektansvarlig lege og de i hans stab
som jobber med studien som har både navnet ditt og studie-identitetsnummeret du er tildelt. Dette innebærer at andre ikke vil kunne spore innsamlet genetisk informasjon som er fremkommet om deg, tilbake til deg. Det tilrettelegges for at dette opprettholdes gjennom hele studien. I tillegg vil din deltakelse i denne studien ikke dokumenteres i din vanlige sykehusjournal.

Vi vil gjerne ha muligheten til å se hvordan det går med deg i fremtiden. Men samtidig ønsker vi at du skal være anonym, spesielt med tanke på genene. Derfor gjør vi sånn som dette: Vi sender de opplysningene som vi får av deg nå i dag, til en utenforstående offentlig institusjon som ikke har noe med studien å gjøre. Om noen år håper vi å kontakte deg på nytt, blant annet for å måle lungefunksjonen din. Så vil vi sende disse dataene til denne utenforstående offentlige institusjonen. De sender dataene i anonymisert form tilbake til oss, slik at de ikke kan spores tilbake til deg. Slik kan vi se på genenes betydning for lungehelse over tid, men samtidig la deg være anonym. Den utenforstående offentlige institusjonen er Kreftregisteret.

Innsyn i din journal
Om du sier deg villig til å være med i denne studien, sier du deg også villig til å gi visse andre enn prosjektansvarlig lege og hans medarbeidere tilgang til din sykehusjournal, hvis du har en slik journal på sykehuset. De andre instanser som kan ha behov for tilgang på din journal er representanter fra offentlige kontrollmyndigheter og representanter fra legemiddelfirmaet, GlaxoSmithKline. Disse trenger å ha tilgang til din journal for å sjekke at opplysninger gitt i studien stemmer med opplysninger i din journal, for å kontrollere studiens kvalitet. Innsynet gjelder for den begrensede tidsperiode studien går over og gjelder for studie-relatert informasjon. Den lege du vanligvis går til (fastlegen) vil få opplysninger om din deltagelse i studien dersom du ikke har noe imot det.

Databearbeidelse
I forbindelse med denne utprøvningen har vi fått tillatelse av Datatilsynet til å opprette et dataregister for å bli i stand til å behandle resultatene på en rask og effektiv måte. Bearbeidelse av dataene vil foregå under kontroll av Universitetet i Bergen og GSK og vil bli overført til et annet land. Universitetet i Bergen og GSK vil ikke gi tilbakemelding til den enkelte deltager, lege, forsikringsselskap eller arbeidsgiver om resultater fra denne type undersøkelse unntatt slike individuelle resultater som er nevnt ovenfor. Resultatene vil bli analysert og brukt av forskere ved Universitetet i Bergen og GSK og samarbeidende institusjoner. Ingen, inkludert deg selv, har krav på resultater fra de genetiske prøvene. Resultatene vil foreligge som forskningsrapport uten at noe kan knyttes til en deltager. Det er Universitetet i Bergen og GSK og de som Universitetet i Bergen og GSK samarbeider med, som eier resultatene fra studien, og som har rett til å bruke informasjonen til sin videre utvikling av medisiner eller annen informasjon som kan gi økonomiske fordeler for institusjonene. Resultatene fra studien kan være vitenskapelige oppfinnelser, og både Universitetet i Bergen, GSK og andre forskere kan komme til å søke om patent for slike oppfinnelser.

Hva vil skje med blodprøven som er tatt?
Blodcellene i blodprøven din inneholder ditt arvemateriale. De vil bli dyrket slik at de gir opphav til mange nye, men identisk like blodceller. På denne måten får forskerne flere blodceller de kan skille ut arvemateriale fra. Dermed får de mer av ditt arvemateriale som kan analyseres ved det laboratoriet som får tilgang til prøven eller blodcellene. Prøven/blodcellene vil bli analysert i utlandet og i Norge. Slik gir din blodprøve opphav til celler som kan brukes i forskning på KOLS i et ubegrenset tidsrom. *(Fortsetter…)*

(…continued from previous page)

If a CT examination is performed, you will get a small dose of radiation, comparable to a flight from Norway to the United States. The more radiation you receive during your life, the greater the risk of cancer and tumors or to cause changes to your genes. If you suspect that you are pregnant you should avoid taking this test.

Possible benefits of participating
You will not have any direct benefit from participating in such a study. The results from this study may become useful for patients with COPD in the future. We can learn more about COPD and we may get information that can make it possible to develop better medication for patients with COPD.
The results will not be ready for several years. Information from the lung function tests will be given to you in writing by a doctor. You will also be informed of the results of the lung X-ray, if it is taken.

Personal information and confidentiality
All personal information is treated confidentially and in accordance with the requirements of the new regulations of Personregisterloven (Personal Registry Act). Blood samples and medical information is identified by a study ID number, and not by your name or social security number. Only the project manager and some of his study staff have access to both your name and study ID number. This means that others will not be able to link the collected genetic information back to you. This policy will be maintained throughout the study. In addition, your participation in this study will not be documented in the normal hospital records.

We'd love to have the opportunity to check up on you in the future. However, we want you to remain anonymous, especially in terms of genes. Therefore, we do like this: We send the information we get from you today to an independent public institution. In a few years we will hopefully contact you again, in order to measure your lung function. Then we will send this data to the independent public institution. They will send the data in an anonymous form back to us, so that they cannot be traced back to you. This way we can study the importance of genes on lung health over time while you remain anonymous. The outside public institution in question is the Kreftregisteret (Cancer Registry).

Access to your medical records
If you agree to participate in this study, you also agree to provide access to your hospital records, if you have such records, to certain others than the project manager and his staff. The other agencies that may need access to your medical records are representatives from public control authorities and representatives from the pharmaceutical company, GlaxoSmithKline. They need access to your records to control that the study information is coherent with the information in your medical records. This access is time-limited for the duration of the study, and concerns only study-related information. The physician you usually see (GP) will get information about your participation in the study if you do not have any objections.

Data Processing
In connection with this study, we have been given permission by the Data Inspectorate to create a data registry to be able to process results in a rapid and efficient manner. The processing of the data will be under the control of the University of Bergen and GSK, and the data will be transferred to another country. The University of Bergen and GSK will not give feedback to each participant, physician, insurance company or employer about the results from this type of investigation other than such individual results mentioned above. The results will be analyzed and used by researchers at the University of Bergen and GSK and collaborating institutions. No one, including yourself, are entitled to the results of genetic tests. The results will be published as a research report without any information that can be related to any single participant. It is the University of Bergen and GSK and their collaborators who owns the results from this study, and who has the right to use this information for development of medicines or other information that can provide economic benefits for the institutions. The study may result in a scientific inventions, and both the University of Bergen, GSK and other researchers may apply for a patent for such inventions.

What will happen to the blood sample that was taken?
The blood cells in your blood sample contain your genetic material. They will be cultivated so that they give rise to many new but identical blood cells. This method gives researchers more blood cells that they can separate genes from. As a result, an increased amount of your genetic material will be available for analysis by the laboratory. The sample / blood cells will be analyzed abroad and in Norway. In this way your blood sample gives rise to cells that can be used in research on COPD in an unlimited period.

(Continues…)

(…fortsatt fra forrige side)

Deltar jeg frivillig? Kan jeg trekke meg?
Deltakelse er helt frivillig. Du kan velge ikke å delta, eller du kan velge å delta, og senere, uten å angi årsak, forandre mening og trekke deg. Dersom du velger å trekke deg fra studien før den slutter, vil den prøven av genene som ble tatt av deg og de celler som er dyrket frem fra den, ødelegges.

Forsikring
Alle deltakere i undersøkelsen er forsikret etter de samme regler som gjelder for pasienter som blir undersøkt og behandlet på Haukeland sykehus. Erstatning for evt. påførte skader som følge av studien vil behandles etter regler for Norsk pasienterstatning. Hvis resultatene av disse undersøkelsene tilsier at du bør gå til legekontroll eller få behandling, vil disse kostnadene bli dekket av det offentlige helsevesenet.

Deltagelse i studien
Du står helt fritt til å bestemme om du vil delta i denne studien. Hvis du velger å delta, kan du trekke deg når som helst uten å angi noen årsak. Dette vil ikke ha noen betydning for den generelle behandling du gis eller for ditt forhold til sykehuset. Dersom du er villig til å delta vil du bli undersøkt /stilt spørsmål som beskrevet tidligere i denne informasjonen, for å finne ut om du passer til å være med i studien. Studien kan stoppes, og da vil du bli informert om dette.
Det vil ikke medføre ekstra kostnader for deg ved å delta i dette prosjektet. Du vil ikke bli betalt for deltagelse, men du vil få refundert dine transportutgifter.
Hvis du i løpet av undersøkelsen har spørsmål angående denne studien og din rettighet som deltager, kan du kontakte en av de nedenfor nevnte legene:

Amund Gulsvik Telefon: 55973242 Prosjektansvarlig Professor, overlege Universitetet i Bergen og Lungeavdelingen, Haukeland sykehus	Per Bakke Telefon: 5597.... Overlege, professor II, Lungeavdelingen, Haukeland sykehus og Universitetet i Bergen	Jan Brøgger Telefon: 55974066 Mobiltelefon: 92867303 Lege, universitetsstipendiat Universitetet i Bergen

Samtykke til å delta i studien
Jeg har mottatt og lest denne informasjonen. Jeg har hatt anledning til å stille spørsmål om studien og hva den innebærer. Jeg er klar over at jeg kan trekke meg når som helst uten å oppgi grunn.
Jeg samtykker med dette til å delta i studien og å bli registrert i en forskningsdatabase i forbindelse med gjennomføring av studien. Jeg samtykker i at jeg som deltager ikke får noen økonomisk kompensasjon og at patent på evt resultater kan søkes av Universitetet i Bergen, GSK og andre forskere.

.....	……	……..
studiedeltagerens navn	studiedeltagerens signatur	Dato for samtykke

Undertegnede bekrefter med dette at studiedeltageren har fått muntlig informasjon, blitt gitt anledning til å lese informasjonen, stille spørsmål angående denne studien, og har fatt tid til å vurdere sin deltagelse før han/hun har undertegnet og datert dette samtykke-skjemaet.

Lege evt. personell som har gitt informasjon og tatt imot samtykke:

……	…….	…….
Navn	Signatur	Dato

Studiedeltageren beholder den gule kopien, studiemedarbeideren den hvite.

(…continued from previous page)

Do I participate voluntarily? Can I withdraw?
Participation is completely voluntary. You can choose not to participate, or you may choose to participate, and then later change your mind and withdraw, without specifying why. If you choose to withdraw from the study before it ends, the samples that were taken from you, including any grown cell cultures, will be destroyed.

Insurance
All participants in this study are insured by the same rules that apply to patients who are examined and treated at Haukeland University Hospital. Compensation for any harm as a result of the study will be treated by the rules for the Norwegian patient compensation. If the results of these investigations suggest that you should see a physician or receive treatment, these costs will be covered by public health care system.

Participation in the study
You are free to decide whether to participate in this study or not. If you choose to participate, you can withdraw at any time without giving any reason. This will have no impact on your general treatment or for your relationship to the hospital. If you are willing to participate, you will be examined / questioned as described previously in this information, to determine that you fulfill the criteria to participate in the study. The study can be terminated, and if so you will be informed.
Participating in this project will not incur any additional cost for you. You will not be paid for participation, but you will be reimbursed your travel expenses.
If you in the course of this investigation have any questions about this study or your rights as a participant, you can contact any of the below-mentioned study physicians:

Amund Gulsvik Telephone: 55973242	Per Bakke Telephone: 5597....	Jan Brøgger Telephone: 55974066 Mobile: 92867303
Project Manager Professor, Consultant University of Bergen and Pulmonary Dept, Haukeland University Hospital	Consultant, Professor Pulmonary Dept, Haukeland University Hospital and University of Bergen	Physician, Research fellow University of Bergen

Consent to participate in the study
I have received and read this information. I have had the opportunity to ask questions about the study and what it entails. I am aware that I can withdraw at any time without giving any reason.
I hereby agree to participate in this study and to be registered in a research database as part of the study. I agree that I as a participant will not receive any financial compensation and that patents on possibly results can be sought by the University of Bergen, GSK and other researchers.

....	.. ..	.. ..
study participant's name	study participant signature	date of consent

The signatory confirms that the study participant has received verbal information and has been given the opportunity to read the information, ask questions about this study and has had extensive time to consider their participation before he / she has signed and dated this consent form.

Study physician or other study personnel that has given information and received the consent:

... ...	.. ..	... ...
Name	Signature	Date

The study participant retains the yellow copy, the study representative retains the white copy

Appendix D

Case-control questionnaire: English translations / Norwegian versions *of selected questions used in papers 1-3*

Smoking history

- Have you ever smoked cigarettes? ('No' means less than 1 cigarette a day for 1 year) (Yes, No, Don't know)

If yes:

- Do you smoke cigarettes now (as of 1 month ago)? (Yes, No, Don't know)
- At what age did you first start smoking regularly? (Age)
- If you have stopped smoking cigarettes completely, how old were you when you stopped? (Age)
- How many cigarettes do you now smoke per day? (Number)
- Historically, what is the average number of cigarettes that you smoked per day? (Number)

- Har du noensinne røykt sigaretter? ("Nei" betyr mindre enn 1 sigarett om dagen i 1 år)

(Ja, Nei, Vet ikke)

Hvis ja:

- Røyker du sigaretter nå (dvs for 1 måned siden)? (Ja, Nei, Vet ikke)
- Hvor gammel var du da du først begynte å røyke regelmessig? (Alder)
- Hvis du har sluttet helt å røyke sigaretter, hvor gammel var du da du sluttet? (Alder)
- Hvor mange sigaretter røyker du nå per dag? (Antall)
- På den tiden du røykte, hvor mange sigaretter pleide du å røyke per dag i gjennomsnitt? (Antall)

Asthma

- Have you had any of the following:
- Asthma? (Yes, No, Don't know)

If yes:

- Was this confirmed by a doctor? (Yes, No, Don't know)

- Har du hatt noen av de følgende:
- Astma? (Ja, Nei, Vet ikke)

Hvis Ja:

- Ble dette bekreftet av lege? (Ja, Nei, Vet ikke)

Exacerbations

- Have you had treatment with antibiotics for a lung disease during the last 12 months? (Yes, No, Don't know)

If yes:

- How many times?

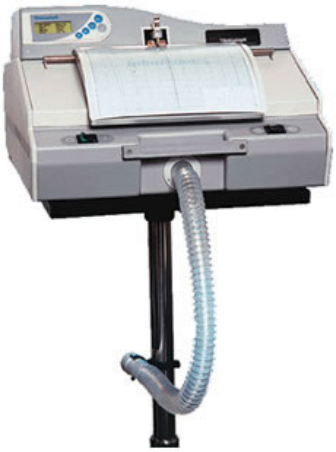
- Har du få tt behandling med antibiotika for en lungesykdom i løpet av de siste 12 månedene? (Ja, Nei, Vet ikke)

Hvis JA:

- Hvor mange ganger?

Appendix E

Technical specifications for Vitalograph 2160 Gold Standard Plus



Technical Specifications ... Vitalograph® GoldStandard +	
Parameters measured	configurable by operator
Measuring principle	dry wedge type bellows
Measuring accuracy	better than +3%/50mL (ATS 1994)
Linearity	litre-by-litre system
Size	460 x 465 x 290mm
Weight	9.1 Kg
Back pressure	<2.5cmH2O/L/s (Complies to ATS 1994)
Volume measurement	direct
Maximum recorder volume	8 L BTPS @ 23°C (Using 12-s charts)
Display	4 lines x 20 chs LCD
Power supply	10v DC via PowerSAFE
Maximum test duration	12 s dynamic (30-s VC)
Leakage rate	0.038L/min max. @ 4L, 300g load
Recording speed	20mm/sec over 12 sec
Timing accuracy	±1% of measured time (ATS 1994)
Activation volume	0.04 L
Operating temp. (physiological)	15 – 37°C
Safety standards	CE mark, EN60601-1/2
Spirometry standards	ATS ’94, ERS ‘93

http://www.vitalograph.ie/products/gold_standard_range

Appendix F

Technical specifications for GE LightSpeed Ultra CT Scanner

Product Data
Release December 2001
Page 13-15

Internet—http://ge-medicalsystems.com/
GE Medical Systems-Europe: Paris, France
Fax: 33 1 30 70 94 35
GE Medical Systems-Asia:
Tokyo, Japan - Fax: 81 425 85 5490
Hong Kong - Fax: 852 2559 3588

PO Box 414 Milwaukee WI 53201 USA

CT LightSpeed™ Ultra

Volume CT Scanner System

System Components

Gantry:
Advanced slip ring design continuously rotates generator, tube, detector and data acquisition system around the patient.

- Aperture: 70 cm
- Tilt: ± 30°
- Tilt Speed: 1°/sec.
- Focus to Detector: 95 cm
- Focus to Isocenter: 54 cm
- Maximum SFOV: 50 cm
- Rotational Speeds: 360° in 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0 and 4.0 sec.
- In-room Gantry controls (Front Right, Front Left, Back Right, Back Left) place the patient at the center of attention
- Programmable start timer and display allow operator to start the exam from the patient's side and safely exit the scan room
- Breath-in lights with goal oriented countdown display improve patient breath hold compliance and avoid retakes
- Remote gantry tilt controls at the operator console reduce trips between the scanner and the console

Scan plane towards front of gantry for improved positioning access.

Biopsy and interventional studies have been facilitated through a more streamlined gantry shroud, and bilateral table/gantry controls and gantry display that maximize maneuverability while working next to the gantry.

Laser Alignment Lights:
- Define both internal and external scan planes to ± 1 mm accuracy.
- Operate over full range of gantry tilt; activated any time during exam (with tube stationary).
- Coronal light remains perpendicular to axial light as gantry tilts.

Visual readout is easy to read from the table side or from the operator console.

Table:
- Single table, cantilever design with wide height range
- Vertical Range: 51 cm to 107 cm
- Vertical Scannable Range: 88 cm to 107 cm
- Elevation Speeds: 5 mm/sec and 40 mm/sec
- Horizontal Range: 170 cm
- Horizontal Scannable Range: 170 cm metal-free (axial) and 160 cm metal-free (helical & Scout)
- Horizontal Speed: Up to 100 mm/sec

- Table automatically recenters on scan plane with changes in vertical position (after setting internal landmark with alignment lights on)
- Table Load Capacity:
  - 180 kg (400 lb) with +/- 0.25 mm positional accuracy
  - 205 kg (450 lb) maximum allowed with normal operation and +/- 1 mm positional accuracy
- Controls on gantry for elevation and cradle incrementation. Foot pedals on both sides of table for fast elevation. Cradle position controlled from OC for prescribed scans.

X-Ray Tube:
Performix Ultra Metal-Ceramic Tube Unit. Design optimized for exams requiring a large number of scans without tube cooling.
- Heat Storage Capacity: 6.3 MHU
- Heat Dissipation:
  - Anode (max) 840 KHU/min
  - Casing (cont) 300 KHU/min
  - Tube Unit: 6.9 kW continuous for 10 minutes
- Dual Focal Spots:
  - Small Focal Spot: 0.7 (W) x 0.6 (L) nominal value (IEC 336/93) 0.9 mm (W) x 0.7 mm (L) (traditional methodology)
  - Large Focal Spot: 0.9 (W) x 0.9 (L) nominal value (IEC 336/93) 1.2 mm (W) x 1.2 mm (L) (traditional methodology)
- Maximum Power: 53.2 kW
- Beam collimated to 55° fan angle.

Average time to replace tube: < 10 hours

High Voltage Generation
- High-frequency on-board generator. Continuous operation during scan.
- 53.2 kW output power.
- kVp: 80, 100, 120, 140 kVp.
- mA: 10 to 440 mA, 10 mA increments

Maximum mA for each kVp selection:

kVp	Max mA
80	400
100	420
120	440
140	380

HiLight Matrix Detector:
16 rows of 1.25 mm thickness, each containing 880 active patient elements; 32 reference elements.
1.0-mm detector element spacing.

7 modes of data output:
- 1 x 1.25 mm (uses 1 row at center)
- 4 x 1.25 mm (uses center 4 rows)
- 4 x 2.5 mm (uses center 8 rows)
- 4 x 3.75 mm (uses center 12 rows)
- 4 x 5 mm (uses all 16 rows)
- 8 x 1.25 mm (uses center 8 rows)
- 8 x 2.5 mm (uses all 16 rows)

70 % geometric efficiency; 98 % absorption efficiency.

Data Acquisition System:
6144 available input channels.
1640 Hz maximum sample rate.

Effective analog to digital conversion range greater than two million to one.

Scan/Control Unit:
Located in base of Operator Console.
Operator Console:
- Size: 48 inch (1220 mm) wide x 40.5 inch (1030 mm) deep x 49.5 inch (1260 mm) high
- Front and back work surfaces can be set during installation within a range of vertical heights that help accommodate a variety of siting requirements

Host Computer:
- Silicon Graphics, Inc. Octane Workstation
- 300-MHz CPU with 2 MB cache.
- 64-bit microprocessor. Dual R12K processor with Direct3D option.
- RISC architecture
- ≥ 17 SPECfp95
- ≥ 9.3 SPECint95
- 512 MB ECC SDRAM standard.

Image Processor:
- Silicon Graphics, Inc. IMPACT Graphics Engine
- 4 MB TRAM (Texture Memory)
- 60 Million trilinear interpolations per second

Image Reconstruction Engine (Pegasus)
- Custom-designed special purpose CT Image Generator
- Pipelined parallel processing allows 12 views to be back-projected simultaneously
- GE-patented IG ASICS provides 7.5 GFLOPS for back projection and IBO acceleration
- 32-bit floating point data format
- IG DSP's rated at 1900 MFLOPS

Software Architecture:
- Software architecture based on industry standards and client-server design
- Approximately 25 server processes running within system architecture at any time
- Third generation object-oriented software development

Peripherals:
- Main system (host) disk drive:
  - High Performance Drive
  - 9 GB, 3.5 inch form factor
  - 10,000 RPM
  - UltraSCSI interface
  - Assigned to applications software and image files
  - Stores 3700 uncompressed 512 image files

- Second system disk drive (Image Disk)
  - High Performance Drive
  - 9 GB, 3.5 inch form factor
  - UltraSCSI interface
  - Assigned to image files only
  - 9 GB stores 16,300 uncompressed 512 image files; brings total system storage to 20,000 uncompressed 512 images

- Scan data disk drive:
  - High Performance Drive
  - 18 GB, 3.5 inch form factor
  - UltraSCSI interface
  - Assigned to 2000 scan data files and calibration files
  - Each scan file approximately 6.14 MB

- Standard MOD drive:
  - Magnetic Optical Disk Drive
  - Erasable, rewritable media
  - 2.3 GB, 3.5 inch form factor
  - Assigned to DICOM 3.0 format image file, scan file, and protocol file storage/retrieval (one file type per side)
  - Stores 4700 lossless JPEG compressed 512 image files per side
  - Stores 350 uncompressed scan data files per side
  - Approximately 2 sec storage or retrieval time per 512 image
  - Off-line retrieval of image and scan files. Images may be viewed as soon as they are restored from MOD

- CD-ROM drive:
  - Integrated in front of operator console for easy access
  - 32X or greater rotational mode
  - 0.65 GB, 5.25 inch half height form factor
  - Assigned to Sherlock on-line computerbased training and loading software

- 2 x CRT Color monitors*:
  - 21 inch diagonal width
  - 1280 x 1024 dot resolution
  - Non-interlaced, flicker-free presentation
  - 76 kHz Horizontal deflection frequency
  - 72 Hz Vertical deflection frequency
  - Sync on green

- 2x Flat Screen Color Monitors:
  - 46cm (18 inch) LCD monitors
- Scan control keyboard assembly with intercom speaker, mic and volume controls; English language keyboard
- Global modem to allow Insite connectivity.
- 3-Button Mouse
- 3-Button Trackball

Image Networking:
- Standard auto-configuring
- 100BaseT/10BaseT Ethernet (UTP connection)
- Direct network connection; multi-suite Ethernet card not required for gateway out of suite
- Protocols supported:
  - DICOM 3.0 network send (one IP address at a time) & receive, pull/query, and storage commitment push;
  - AdvantageNet (GenesisNet) point-to-point
  - send, receive and pull/query (no broadcast);
  - InSite point-to-point;
  - TCP/IP (for system administration).

Appendix G

Online supplements for Papers II and III that are not available elsewhere in this thesis

Paper II, Table E1

Table E1. Adjusted Cox regression analysis. Risk for lung cancer in all subjects, N=852.

	‘HRR	95% CI
Sex	1.10	0.60-2.00
Age	1.02	0.99-1.06
Pack Years	1.01	1.00-1.02
Current smokers	0.74	0.42-1.30
Age of onset of smoking	0.99	0.92-1.05
^PB FEV1 pp	0.95	0.81-1.12
§BMI (kg/m^2)	**0.92***	**0.87-0.98**
Asthma	1.18	0.60-2.35
~AECOPD, 1 or more	**2.55***	**1.25-5.21**
AECOPD#asthma	**0.34***	**0.11-0.98**

‘Hazard Rate Ratio, ^Post-bronchodilator FEV1 percent predicted, divided by 10. §Body mass index, ~Acute exacerbations in COPD, # interaction between AECOPD and asthma * p<0.05, ** p<0.01.

Table E2

Table E2. Adjusted Fine & Gray regression analyses. Mortality as competing risk. Probability of having lung cancer in COPD patients with and without asthma

	No asthma		Asthma	
	‘SHRR N = 430	95 % CI	‘SHRR N = 422	95 % CI
Sex	1.65	0.72 - 3.77	0.74	0.31 - 1.79
Age	1.01	0.99 - 1.04	1.00	0.96 - 1.03
Pack Years	1.01	0.99 - 1.03	1.01	0.99 - 10.3
Current smokers	0.67	0.30 - 1.50	0.81	0.32 - 2.05
Age of onset of smoking	0.95	0.84 - 1.07	1.01	0.93 - 1.10
^PB FEV1 pp	1.05	0.84 - 1.30	1.02	0.80 - 1.30
§BMI (kg/m^2)	**0.89****	**0.82 - 0.97**	0.98	0.91 - 1.05
~AECOPD, 1 or more	**2.60****	**1.21 - 5.56**	0.88	0.38 - 2.05

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

Paper III, Table E1

Table E1. Positive predictive value (PPV) and negative predictive value (NPV) as well as sensitivity and specificity of the COPD-LUCSS and the NLST criteria for lung cancer among COPD patients

	PPV	NPV	Sensitivity	Specificity
COPD-LUCSS, (95% C.I.)	9% (7-11)	96% (93-98)	70 %	51 %
NLST criteria, (95% C.I.)	10% (7-14)	95% (93-97)	48 %	70 %

COPD-LUCSS: Chronic Obstructive Pulmonary Disease – Lung Cancer Screening Score
NLST: National Lung Cancer Screening Trial score say that this goes for the whole population

Table E2

Table E2. Logistic regression showing association of COPD-LUCSS and lung cancer as well as NLST criteria and lung cancer in smokers with COPD

	Ever-smokers with COPD N=422
COPD-LUCSS	2.5* (1.1-5.8)
NLST	2.2(1.0-4.7)

Data are presented as Odds ratio (95% CI). High Risk vs Low Risk of the COPD-LUCSS (chronic obstructive pulmonary disease lung cancer screening score) and NLST (national lung cancer screening trial). *: p<0.05; **: p<0.01; ***: p<0.001

Table E3

Table E3. Distribution of lung cancers according to the COPD-LUCSS and the NLST criteria, with ten- and eight-years follow-up.

	Lung cancer followed ten years		Lung cancer followed eight years		
COPD-LUCSS	No	Yes	No	Yes	Total
Low risk	201	9	202	8	210
High risk	191	21	193	19	212
Total	393	30	395	27*	422

	Lung cancer followed ten years		Lung cancer followed eight years		
NLST criteria	No	Yes	No	Yes	Total
Low risk	275	15	276	14	290
High risk	117	15	119	13	132
Total	393	30	395	27*	422

* For the logistic regression analysis, the follow-up was set to eight years to enable the same follow-up for each individual. Cox regression enables censoring. Ten years follow-up was therefore used in the Cox regression. There were 30 cancer cases with the total follow-up time.

PAPER I

PAPER II

Acute exacerbations of COPD and risk of lung cancer in COPD patients with and without coexisting asthma.

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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, 6) (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 a study of 433 COPD patients and 279 healthy controls, AECOPD was not related to increased incidence of lung cancer during nine years of follow-up (7).

Patients with coexisting asthma have often been excluded from COPD studies. This was also the case with the study of Husebø et al. (7). COPD patients with coexisting asthma may have a different exacerbation phenotype compared to COPD patients without coexisting asthma

(9). Hence, the risk of lung cancer from AECOPD might vary by the presence of a coexisting asthma (10).

We had access to a population-based cohort of subjects with COPD, which includes information regarding asthma diagnosis as well as AECOPD the year before inclusion. This information was linked with data from the Cancer Registry of Norway (11) in order to 1) explore whether AECOPD is associated with an increased risk of lung cancer during ten years follow-up, and 2) whether the risk of lung cancer due to AECOPD differs based on coexisting 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 comprise 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.

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 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 methods were 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 report 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 asthma on lung cancer was also tested.

Furthermore, analyses stratified by 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), which did not differ significantly between those with and without exacerbations.

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

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 ten years was that AECOPD was only significantly associated with increased risk of lung cancer in COPD patients without coexisting 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). Carr et al. followed a cohort of subjects with and without COPD. 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 ten 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 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 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 coexisting asthma.

This finding could have several explanations. First, one recent retrospective study found that coexisting asthma in COPD patients is associated with decreased risk of lung cancer (10). This could indicate that COPD patients with coexisting 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 propagation of genetic errors (23). Patients with coexisting 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 (24). 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 (25) 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 (26). 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 (27, 28). Some bacteria and more viruses play an essential part in cancer development of other types of cancer (29, 30). 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 asthma smoked less than COPD patients without 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 asthma had higher educational attainment than the group with 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 (31). 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, the exacerbations were questionnaire-based, and we do not have data on the type of exacerbation or samples of eosinophils. Third, the asthma diagnosis was questionnaire-based and presented 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 prevalence of asthma in this population of subjects with COPD is in line with other epidemiological studies (32-35), but higher than in clinical trials (36, 37). 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 (38). 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 (39). Nevertheless, most randomized control trials have had recruitment criteria based on age and smoking history alone (40-45). 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 and COPD patients with coexisting asthma, are needed to better understand

which mechanisms link COPD and lung cancer. As we learn more about the clinical phenotypes of COPD, these might help target those COPD patients at the highest risk and determine who to include in screening trials.

Conclusion

Exacerbations of COPD is associated with an increased risk of lung cancer in those without asthma, but not in those with a history of asthma.

Tables and figures

Table 1. Baseline characteristics by 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)	0.504
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)	0.468
~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)	0.528
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 percent predicted.

Table 2. Unadjusted Cox regression analyses. Risk for lung cancer in COPD patients with and without 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 percent predicted, divided by 10. §Body mass index, ~Acute exacerbations in COPD, * p<0.05, ** p<0.01.

Figure 1. Survival estimates for lung cancer by AECOPD in COPD patients without (A) and with asthma (B).

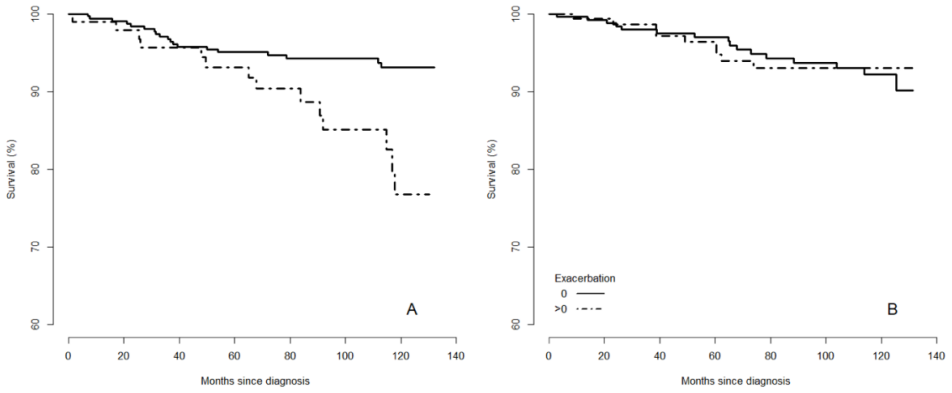
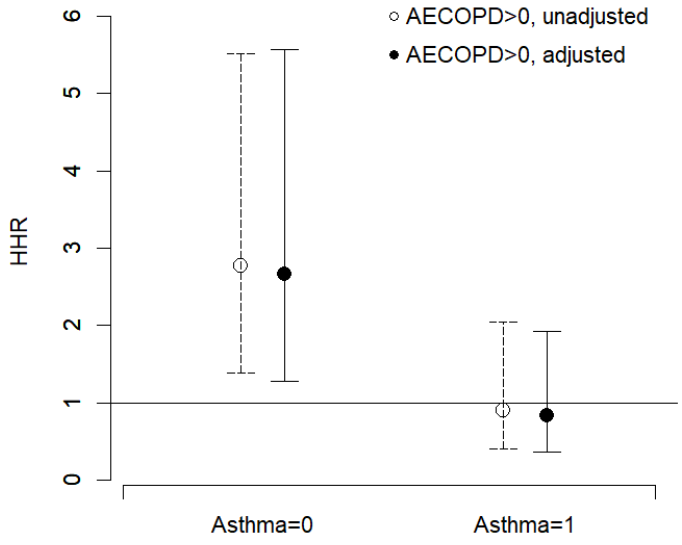


Figure 2. Unadjusted and adjusted Cox regression analyses. Risk for lung cancer in COPD patients without and with asthma



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

Online supplement

Table E1. Adjusted Cox regression analysis. Risk for lung cancer in all subjects, N=852.

	'HRR	95% CI
Sex	1.10	0.60-2.00
Age	1.02	0.99-1.06
Pack Years	1.01	1.00-1.02
Current smokers	0.74	0.42-1.30
Age of onset of smoking	0.99	0.92-1.05
^PB FEV1 pp	0.95	0.81-1.12
§BMI (kg/m^2)	**0.92***	**0.87-0.98**
Asthma	1.18	0.60-2.35
~AECOPD, 1 or more	**2.55***	**1.25-5.21**
AECOPD#asthma	**0.34***	**0.11-0.98**

'Hazard Rate Ratio, ^Post-bronchodilator FEV1 percent predicted, divided by 10. §Body mass index, ~Acute exacerbations in COPD, # interaction between AECOPD and asthma * p<0.05, ** p<0.01.

Table E2. Adjusted Fine & Gray regression analyses. Mortality as competing risk. Probability of having lung cancer in COPD patients with and without asthma

	No asthma		Asthma	
	'SHRR	95 % CI	'SHRR	95 % CI
	N = 430		N = 422	
Sex	1.65	0.72 - 3.77	0.74	0.31 - 1.79
Age	1.01	0.99 - 1.04	1.00	0.96 - 1.03
Pack Years	1.01	0.99 - 1.03	1.01	0.99 - 10.3
Current smokers	0.67	0.30 - 1.50	0.81	0.32 - 2.05
Age of onset of smoking	0.95	0.84 - 1.07	1.01	0.93 - 1.10
^PB FEV1 pp	1.05	0.84 - 1.30	1.02	0.80 - 1.30
§BMI (kg/m^2)	**0.89****	**0.82 - 0.97**	0.98	0.91 - 1.05
~AECOPD, 1 or more	**2.60****	**1.21 - 5.56**	0.88	0.38 - 2.05

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

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PAPER III

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ORIGINAL ARTICLE

WILEY

Comparison of two lung cancer screening scores among patients with chronic obstructive pulmonary disease: A community study

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Abstract

Introduction: Based on the National Lung Cancer Screening Trial (NLST), guidelines on screening programs for lung cancer have recommended low-dose computed tomography (LDCT). De Torres et al made a score for COPD patients (COPD-LUCSS) to improve their selection criteria.

Objective: To examine and compare the discriminating value of both scores in a community-based cohort of COPD patients.

Methods: Four hundred and twenty-two ever-smokers with COPD from the GenKOLS study in Bergen were merged with the Cancer Registry of Norway. We divided the patients into groups of high and low risk according to the COPD-LUCSS and the NLST criteria. Cox regression and logistic regression were used to analyse the associations between the scores and lung cancer. We used Harrell's C and area under the curve (AUC) to estimate discriminating values and to compare the models.

Results: Hazard ratio for the high risk vs the low risk in the COPD-LUCSS was 3.0 (1.4-6.5 95% CI), $P < 0.01$. Hazard ratio for the NLST criteria was 2.2 (95% CI 1.1-4.5), $P < 0.05$. Harrell's C was 0.63 for the COPD-LUCSS and 0.59 for the NLST selection criteria. AUC was 0.61 for COPD-LUCSS and 0.59 for NLST criteria. Comparing tests showed no differences ($P = 0.76$).

Conclusion: Although the COPD-LUCSS and the NLST criteria were associated with increased risk of lung cancer, the AUC and Harrell's C values showed that these models have poor discriminating abilities in our cohort of COPD patients. The COPD-LUCSS was not significantly better than the NLST criteria.

KEYWORDS
COPD, epidemiology, lung cancer, screening

1 | INTRODUCTION

Guidelines on screening programs for lung cancer in smokers recommend using low-dose computed tomography (LDCT) of the chest.[1] These recommendations are mainly based on the National Lung Cancer Screening Trial (NLST), which observed that using LDCT might reduce lung cancer mortality by at least 20%.[2] The NLST screening selection criteria included individuals between 55 and 74 years of age with a smoking history of at least 30 pack years. The subjects were either current smokers or had quit within the last 15 years.

Since the NLST article was published in 2011, several studies have tried to improve the NSLT criteria.[3-5] De Torres et al[5] also created a score, the COPD-LUCSS (chronic obstructive pulmonary disease—lung cancer screening score). This score included the presence of emphysema, age above 60 years, pack years above 60 and body mass index (BMI) below 25 as predictors and found that this score predicted

lung cancer in patients with chronic obstructive pulmonary disease (COPD) better than the NLST selection criteria.[5] The authors were able to replicate their findings in an independent study population. However, the COPD patients were recruited from two screening cohorts. It may be questioned to which extent their findings are valid in the COPD population at large. They followed their cohort for 3-4 years, and the long-term benefits of their criteria are still unknown.

We had access to a community-based sample of ever-smokers with COPD, all examined with computed tomography of the chest in 2003-2005. This data set was merged with data from the Cancer Registry of Norway,[6] providing data on lung cancer incidence from 2003 to 2013, ie, the population was followed for 8-10 years. We aimed to examine and compare the discriminating ability of the COPD-LUCSS and the NLST criteria in our population-based sample of ever-smokers with COPD.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients were selected from the GenKOLS (Genetic COPD) study in Bergen, Norway. The GenKOLS study recruited subjects from two general population studies and a hospital patient register.[7] The GenKOLS study was conducted from January 2003 to January 2005.[8] Subjects were 40-85 years of age and had a smoking history of 2.5 pack years or more at baseline. COPD was diagnosed when post-bronchodilator FEV1/FVC was <0.70 and FEV1 was <80% predicted. The examination at baseline in 2003/05 included chest CT, pulmonary function tests and questionnaires on smoking habits. The GenKOLS data were merged with the Cancer Registry of Norway[6] with complete data through 2013 ($n = 422$). Details on the study population are described elsewhere.[9]

2.2 | Quantitative interpreted CT

CT scans were performed with a GE LightSpeed Ultra CT scanner at full inspiration using 1-mm slice thickness at 20-mm intervals. The extent of emphysema was assessed using the percentage of lung voxels with X-ray attenuation values (low-attenuation areas, %LAA) less than −950 Hounsfield units (%LAA950). This cut-off has been shown to be accurate for the CT acquisition technique.[10] Percent emphysema for the whole lung was calculated. Emphysema was measured as %LAA950. These measurements were taken from a previous study on the same population examining emphysema and mortality.[11] In our study, those with LAA 3% and above are considered to have emphysema present.

2.3 | The Cancer Registry of Norway

All individuals in Norway diagnosed with cancer of any type are registered in the Cancer Registry of Norway.[6] Registration is obligatory by law, by both clinical doctors and pathologists, thus securing completeness of the registry.[12] The inclusion rate is close to 100%. Subjects who developed cancer during the follow-up in our study were identified in the Cancer Registry of Norway. ICD-10-code C34 defined lung cancers. The data obtained included the time of diagnosis. The Norwegian Data Inspectorate, the Norwegian Directorate of Health and Social Services the Regional Ethical Committee for Medical Research gave permission to use the data.

2.4 | Other variables

Smoking variables included current smoking status, pack years and age at onset of smoking, all self-reported at baseline. Spirometries were performed according to the American Thoracic Society standards.[13] Reference values for FEV1 and FVC were local.[14] COPD patients were categorized into grades 2-4 according to GOLD2007 classification, as defined by FEV1 in the percent predicted.[15]

2.5 | Statistical analysis

The patients were divided into groups of high and low risk according to the COPD-LUCSS and the NLST criteria[1,2] (Table 1). The association between the COPD-LUCSS and lung cancer, as well as the NLST criteria and lung cancer, was assessed by Cox proportional hazards regression, followed by Harrell's C concordance statistics estimates to measure discrimination.[16] In order to compare the models objectively, we also used logistic regression with 8 years of follow-up. We used lung cancer as the outcome, followed by post hoc receiver operating curve (ROC) and intra model area under the curve (AUC) comparisons for the COPD-LUCSS and the NLST scores.[17] To obtain the ROC curves and AUC comparisons, we used the Stata commands *lroc* and *roccom.* This method provides a χ^2 test for the difference in AUCs between two estimated models using the same set of observations. An AUC varies between 0 and 1. A value of 1 indicates a perfect diagnostic tool with 100% sensitivity and 100% specificity, whereas an AUC of 0.5 implies no discrimination. All analyses were performed using STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, Texas: StataCorp LP), and the two-sided significance level was set to 0.05 for all analyses.

3 | RESULTS

A total of 422 subjects were included in this study. Characteristics are described in Table 2. Applying the

TABLE 1 Variables included in the COPD-LUCSS and in the NLST selection criteria

COPD-LUCSS	
BMI < 25	1 point
Pack years history > 60	2 points
Age > 60 years-old	3 points
Radiological emphysema: yes	4 points
Total	10 points
NLST inclusion criteria	
Pack years > 30	
Age 55-74 years	
Current smoker or quit smoking within the previous 15 years	

Abbreviations: COPD-LUCSS, Chronic Obstructive Pulmonary Disease—Lung Cancer Screening Score; NLST, National Lung Cancer Screening Trial.
Notes: In the COPD-LUCSS, the low-risk category includes those with 0-6 points. The high-risk category includes those with 7-10 points.
In the NLST, those with all the mentioned criteria are considered as high risk. Those with two or less of the mentioned criteria are considered low risk.

TABLE 2 Characteristics by sex

	Female	Male
Subjects, *n*	151	271
Years of age, mean (SD)	62.1 (8.9)	65.1 (9.4)
Current smokers (%)	53.6	46.5
Pack years, median (25/75 percentile)	22.5 (16/33)	30.8 (21/44)
Age of onset of smoking, mean (SD)	20.2 (6.3)	17.4 (4.0)
Emphysema[a], mean (SD)	9.7 (11.8)	12.5 (11.8)
Lung cancer (%)	6.6	7.4
BMI[b] (kg/m^2), mean (SD)	25.1 (5.7)	25.8 (4.2)
PB FEV1[c] pp, mean (SD)	53.2 (16.2)	52.8 (17.3)

[a]Emphysema measured in % pe950.
[b]Body mass index.
[c]Post-bronchodilator FEV1 percent predicted.

COPD-LUCSS, 212 of the 422 individuals were ascribed to the high-risk category and 210 to the low-risk category. Of those in the high-risk group, 21 individuals (9.9%) were diagnosed with lung cancer during the follow-up. The corresponding figures in the low-risk group were 9 individuals (4.3%). Using the NLST criteria, 132 of the 422 subjects were characterized as high risk and 290 as low risk. In the high-risk group, 15 (11.4%) got lung cancer. In contrast, 15 out of 290 (5.2%) were diagnosed with lung cancer in the low-risk group. Positive predictive values (PPV) and negative predictive values (NPV), as well as sensitivity and specificity, are shown in the supporting information (Table S1).

Cox regression analysis showed that both the COPD-LUCSS and the NLST criteria were significantly associated with lung cancer in our population of ever-smokers. Hazard ratio for the high risk vs the low risk in the COPD-LUCSS was 3.0, 95% confidence interval (CI) was 1.4-6.5, $P < 0.01$. Hazard ratio for the NLST criteria, high risk vs low risk, was 2.2, 95% CI 1.1-4.5, $P < 0.05$. Harrell's C concordance statistic estimates were 0.63 for the COPD-LUCSS and 0.59 for the NLST selection criteria.

Logistic regression with a follow-up of 8 years showed similar results as the Cox regression (Table S2). The AUC values were 0.61 for the COPD-LUCSS and 0.59 for the NLST selection criteria (Figure 1). There was no significant difference between the AUC values of these criteria, $P = 0.76$. The distribution of lung cancers in each group is shown in the supporting information Table S3.

4 | DISCUSSION

In this study, that comprised a community-based cohort of ever-smokers with COPD, we observed that: (1) although both the COPD-LUCSS and the NLST selection criteria are significantly associated with an increased risk of lung cancer, the models do not discriminate well; (2) there were no significant differences in the ability of discrimination between the

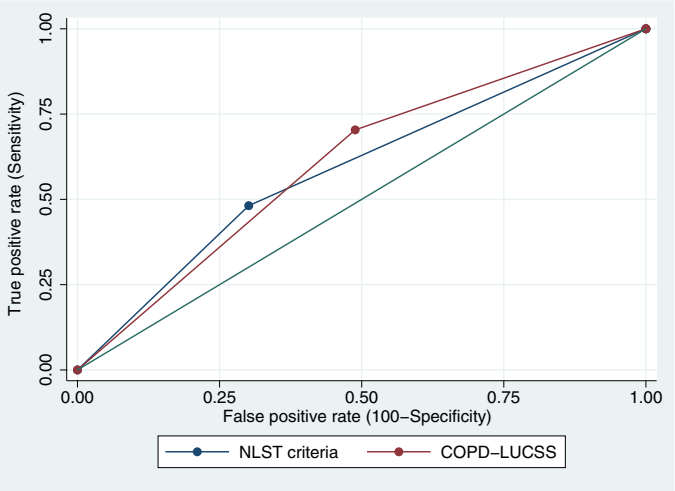

FIGURE 1 ROC curve of the COPD-LUCSS and the NLST criteria in ever-smokers with COPD

COPD-LUCSS and the NLST criteria; (3) even in the low-risk groups of both the criteria, about 4%-5% of the patients developed lung cancer.

Our finding that the COPD-LUCSS is associated with lung cancer among COPD patients is in line with the results of de-Torres et al[5] We have extended the current knowledge by showing that similar results are found in a COPD population that is not sampled through lung cancer screening programs and therefore apply to the COPD population at large. Moreover, we had a follow-up of 10 years, while de-Torres followed their cohort for 5 years. Compared with the populations used by de Torres et al,[18,19] our COPD population was older (mean age 64 years vs 61 years), had a lower overall cigarette consumption (27 pack years vs 43 and 53 pack years) had a lower mean FEV1 (53% of predicted vs 79% and 71% of predicted).

The variables in the COPD-LUCSS were selected through Cox regression and the cut-off values were selected by dividing each variable into quartiles or quintiles. The best cut-off values were chosen by visual assessment.[5] Further, de Torres et al found that the COPD-LUCSS was better than the NLST selection criteria. This was examined by visual comparison of the Kaplan-Meier curves. However, they did not test this statistically. We used an objective test showing no significant difference in our data. Moreover, the AUC values remained between 0.59 and 0.61, indicating approximately the same poor discriminating values for both the COPD-LUCSS and the NLST criteria.[20] Although both criteria are associated with lung cancer, it should be noted that 30% and 50% of the lung cancers occurred in the low-risk group. This is illustrated in Table E3. One could therefore argue that the models in their current form should not be used to select individuals for lung cancer screenings.

We aimed to study the discriminative abilities of the scores, as measured by AUC and Harrell's C. Discrimination is useful in a diagnostic setting to separate people with disease from people without.[21] A predictive model with poor discriminative ability will not be of any use even with good calibration. Hence, we did not assess calibration herein.

More accurate models than the COPD-LUCSS and the NLST criteria are needed. Such a model might include variables like socioeconomic status, ethnicity, family history of lung cancer and occupational airborne exposure.[22] In the future, models including genetic or biomarker-based predictors may lead to further enhancement of lung cancer prediction. The ultimate goal is to create a model that would lead to a high number of lung cancers detected by number of persons screened and a low number among those not screened. For screening tests, it is very important to have high specificity and a high NPV. This is to avoid a high number of false negative results. We are however willing to tolerate a small number of false positive results.[23] Furthermore, the PPV for both tests were 9%-10%, indicating that only a few of those with positive test results actually have the disease. The NPV for both tests was 95%-97% indicating that most of those with a negative test will not have lung cancer. However, the PPV and NPV are influenced by the prevalence of the disease. The more rare the cancer is, the more sure we can be that a negative predictive value indicates no abnormality, and the less sure we can be that a positive predictive value really indicates an abnormality.[24]

The discriminative abilities of both the models are poor, even when evaluated in the same sample used to fit each model. The poor discriminating ability of the COPD-LUCSS and the NLST criteria suggest that these scores might not be suitable as screening guidelines. Screening is a large economic burden on the health care budgets and one should also

consider the psychological effects of a false positive or a false negative result. The NLST screening trial found that 96.4% of the positive findings with low-dose CT were false positives.[2] One might also picture a false feeling of safety among patients and doctors regarding those in the low-risk group.

The strengths of this study are as follows. First, the participants were not sampled from a cancer screening trial, but from a community-based sample followed for more than 4000 person years. Second, the study was prospective in design. Hence, all the lung cancers were diagnosed after the CT scans and examinations were performed. Third, the CT scans were assessed for emphysema through a quantitative examination, avoiding any observer bias. Finally, the diagnoses of lung cancer were obtained from the Cancer Registry of Norway which has a near 100% inclusion rate and is based on a histologically verified diagnosis of the cancer.

A few limitations should also be mentioned. First, the number of lung cancers diagnosed in the study population was small. Second, the CT scans were acquired using a high-resolution CT technique, which was common during the time of the data acquisition for this study. However, all the CT scans were performed using a standard protocol and the measurements of emphysema have been shown to be reproducible using a standard protocol.[25] Third, the study did not include COPD patients diagnosed with GOLD grade 1, which in some studies have shown to have the highest incidence of lung cancer.[26]

Although the COPD-LUCSS and the NLST criteria were associated with increased risk of lung cancer, the AUC values show that these models have poor discriminating abilities in our cohort of COPD patients. More research is needed in order to find better predictive models. The COPD-LUCSS was not significantly better than the NLST criteria in this cohort.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

AAG and MG performed the statistical analyses, drafted and revised the paper.

AG and PSB designed the study, took part in the data collection, drafted revised the paper.

ETHICS

The Regional Ethical Committee for Medical Research approved the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Errata for
Chronic obstructive pulmonary disease and risk of lung cancer

Ane Aamli Gagnat

Thesis for the degree philosophiae doctor (PhD)

at the University of Bergen

_____ _____

(date and sign. of candidate) (date and sign. of faculty)

Errata

Methods section of this thesis, 3.3.3 Paper III

I wrote “An ideal score or model will always be able to classify those who will develop the disease in one category, and those who will not develop the disease in another. A model’s ability to do just that is called discriminatory ability (95).” This is, however, wrong and should have been, “An ideal score or model will always be able to classify those who will develop the disease in one category, and those who will not develop the disease in another. A model’s ability to do just that can be described by both discrimination and calibration. The discriminatory ability of a model refers to its ability to separate those at high risk from those at low risk of an event.”

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