Incidence of non-pulmonary cancer and lung cancer by amount of emphysema and airway wall thickness: a community-based cohort

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ABSTRACT There is limited knowledge about the prognostic value of quantitative computed tomography (CT) measures of emphysema and airway wall thickness in cancer.

The aim of this study was to investigate if using CT to quantitatively assess the amount of emphysema and airway wall thickness independently predicts the subsequent incidence of non-pulmonary cancer and lung cancer.

In the GenKOLS study of 2003–2005, 947 ever-smokers performed spirometry and underwent CT examination. The main predictors were the amount of emphysema measured by the percentage of low attenuation areas (%LAA) on CT and standardised measures of airway wall thickness (AWT-PI10). Cancer data from 2003–2013 were obtained from the Norwegian Cancer Register. The hazard ratio associated with emphysema and airway wall thickness was assessed using Cox proportional hazards regression for cancer diagnoses.

During 10 years of follow-up, non-pulmonary cancer was diagnosed in 11% of the subjects with LAA <3%, in 19% of subjects with LAA 3–10%, and in 17% of subjects with LAA ⩾10%. Corresponding numbers for lung cancer were 2%, 3% and 11%, respectively. After adjustment, 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.

This study offers a strong argument that emphysema is an independent risk factor for both non-pulmonary cancer and lung cancer.

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Introduction

Emphysema in patients with chronic obstructive pulmonary disease (COPD) is the strongest known imaging biomarker for lung cancer [1]. COPD is considered a systemic disease, in which 16% of patients show manifestations of systemic inflammation [2]. Given that inflammation in COPD is a potential mechanism for increased lung cancer risk in these patients, one might hypothesise that systemic inflammation in at least some COPD patients implies a higher risk of non-pulmonary cancer. To our knowledge, this hypothesis has not previously been tested [1].

Previous computed tomography (CT) studies have shown a positive correlation between emphysema and lung cancer by qualitative assessment of emphysema [3–7], whereas conflicting results exist concerning emphysema quantified automatically by software [7–9].

Lung CT examinations of patients with COPD also yield information on their airways. Limited data are available regarding whether airway wall thickness, as a marker of airway inflammation, is associated with an increased incidence of lung cancer as well as non-pulmonary malignancies.

We had access to a community sample of subjects with and without COPD with CT scanning of their lungs. These data were merged with data from the Norwegian Cancer Register from 2013 [10] to explore whether the CT-assessed amount of emphysema and airway wall thickness can predict subsequent incidence of both non-pulmonary cancer and lung cancer.

Methods

Study subjects

Subjects were aged 40–85 years and had a smoking history of ⩾2.5 pack-years at baseline. The 947 subjects included in the current study had all participated in the GenKOLS (Genetic COPD) study conducted from January 2003 to January 2005 [11]. They represented approximately half of the GenKOLS sample (n=1909) who received an optional high-resolution CT scan. Of these 947 subjects, 57 had been diagnosed with cancer prior to inclusion and four subjects left the country during follow-up. They were therefore omitted from further analyses. Thus, 886 subjects were eligible for the current analyses: 422 COPD cases and 464 controls. The GenKOLS study recruited subjects from two general population studies [12, 13] and a hospital patient register. Details on the study population are described elsewhere [14]. COPD was diagnosed when the post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio was <0.70 and FEV_1 was <80% predicted. Those without COPD required a post-bronchodilator FEV_1/FVC ⩾0.70 and FEV_1 ⩾80% predicted. The examination at baseline in 2003–2005 included thorax CT, pulmonary function tests and questionnaires on smoking habits.

Quantitative interpreted computed tomography

CT scans were performed with a GE LightSpeed Ultra CT scanner (120 kVp, 200 mA; GE Healthcare, Milwaukee, WI, USA) 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 <−950 Hounsfield units (percentage of low-attention areas (%LAA)). This cut-off has been shown to be accurate for this CT acquisition technique [15]. The percentage of emphysema for the whole lung was calculated. Airway wall thickness is presented as the square root of the wall area for a standardised airway with an internal perimeter of 10 mm. Details on the CT scanning are presented elsewhere [11].

The Norwegian Cancer Register

Every person in Norway diagnosed with cancer of any type is registered in the Norwegian Cancer Register. Registration is obligatory by law, both by clinical doctors and pathologists, thus securing completeness of the registry [10]. The inclusion rate is close to 100%. Thus, subjects who developed cancer during the follow-up in our study were identified from the Norwegian Cancer Register. Lung cancers were defined by International Classification of Diseases 10th Revision (ICD-10) code C34 and non-pulmonary cancer was defined as all cancers outside the lung. The patients' identification numbers were given with permission from the Norwegian Data Inspectorate, the Norwegian Directorate of Health and Social Services and the Regional Ethical Committee for Medical Research. Data obtained included time of diagnosis, cancer histology and stage, and location of cancer at the time of diagnosis.

Other variables

Smoking variables included current smoking status, pack years and age at onset of smoking, all self-reported at baseline. Spirometry was performed according to the American Thoracic Society standards [16]. Reference values for FEV_1 and FVC were local [17]. COPD patients included were categorised as stage 2–4 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification, as defined by the percentage of predicted FEV_1. Further, the new GOLD 2011 guidelines

have an A–D grouping and are based on self-reported dyspnoea and symptoms (Modified British Medical Research Council (mMRC) Dyspnea Scale, COPD Assessment Test (CAT) score) and number of exacerbations in the last 12 months in addition to the percentage of predicted FEV_1 [18].

Statistical analysis

Emphysema measured as %LAA was the main predictor of interest and was categorised into three categories: low (LAA <3%), medium (LAA 3–10%) and high (LAA ⩾10%). With the lack of suggested classifications of %LAA stages, these categories were based on inspection of the quantile plot, as described in a previous study on the same population examining emphysema and mortality [19]. The amount of emphysema was also assessed with %LAA as a continuous independent variable.

The hazard ratios associated with emphysema and airway wall thickness were estimated using Cox proportional hazards regression for cancer diagnoses. Kaplan–Meier plots were constructed. In the multivariate analyses we adjusted for sex, age, smoking status, age of onset of smoking, pack years and percentage of predicted FEV_1. An overall comparison of the distribution of non-pulmonary cancers across the amount of emphysema was performed using Fisher's exact test. The *a priori* decided interactions between both emphysema and airway wall thickness and the variables sex, age, smoking status, pack years and COPD status, respectively, were tested by employing the likelihood ratio test. The proportionality assumption was checked using the post estimation command *estat phtest* in STATA.

All analyses were performed with STATA 13 (Stata Statistical Software: Release 13; StataCorp, College Station, TX, USA), and the two-sided significance level was conventionally set to 0.05 for all analyses.

Results

The subjects comprised 41% women, the mean±SD age was 59.4±10.3 years and 48% had COPD at baseline (table 1). By inclusion criteria, all were ever-smokers. During the 10-year follow-up, 13% were diagnosed with non-pulmonary cancer and 4% with lung cancer, while 0.9% received both diagnoses. Altogether, 88% of those diagnosed with lung cancer had COPD at baseline. Among the COPD patients, about half of those receiving a lung cancer diagnosis had GOLD stage D at baseline. Only 18% of those not diagnosed with cancer had a LAA ⩾10%, whereas the corresponding numbers for those diagnosed with non-pulmonary cancer and lung cancer were 25% and 59%, respectively.

Kaplan–Meier plots show the incidence estimates for non-pulmonary cancers and lung cancer by amount of emphysema (figure 1). Data show that the higher the amount of emphysema, the higher the risk of

TABLE 1 Baseline characteristics by cancer status after follow-up

Characteristics	Pulmonary cancer[#]	Non-pulmonary cancer[#]	Non-cancers
Subjects n	34	119	741
Male	61.8	63.9	57.8
Age years	65.1±6.6	64.4±9.3	58.4±10.3
Current smokers	44.1	30.3	47.8
Age of onset of smoking years	17.9±4.6	18.5±4.5	18.4±5.0
Pack-years, median (IQR)	33.8 (22–50)	22.1 (14–38)	21.0 (12–32)
Subjects without COPD	11.8	47.9	54.5
GOLD stages in COPD cases			
Stage A	20.0	21.7	25.9
Stage B	26.7	45.0	29.9
Stage C	3.3	5.0	7.3
Stage D	50.0	28.3	36.9
FEV_1[¶]	54.3±21.4	75.8±23.5	75.7±24.8
Emphysema %LAA	15.7±13.2	6.9±9.0	5.5±9.5
Emphysema categories			
LAA <3%	26.5	51.3	66.5
LAA 3–10%	14.7	23.5	15.9
LAA ⩾10%	58.8	25.2	17.5
AWT-Pi10 mm	4.83±0.35	4.85±0.32	4.85±0.33

Data are presented as % or mean±SD, unless otherwise indicated. IQR: interquartile range; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; LAA: low-attenuation area; AWT-Pi10: airway wall thickness (square root of wall area for airway with internal perimeter of 10 mm). [#]: 8 persons had both lung cancer and non-pulmonary cancer; [¶]: percentage of predicted post-bronchodilator FEV_1.

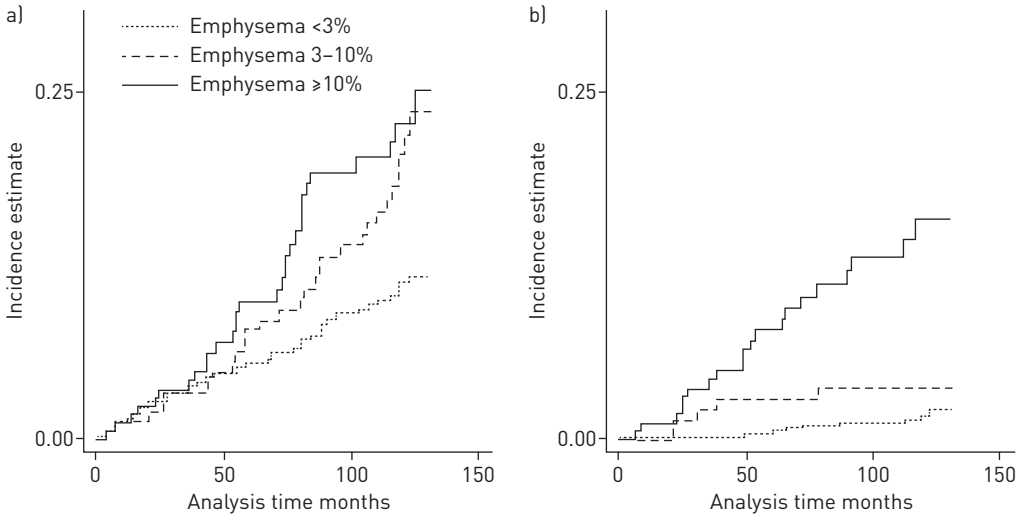

FIGURE 1 Kaplan–Meier curve for the incidence of a) non-pulmonary and b) lung cancer by amount of emphysema. The figure shows censored data.

non-pulmonary cancer and lung cancer. This is consistent with crude analyses, not accounting for censoring. Without taking censoring into account, 11% of the subjects in the lowest %LAA emphysema category got non-pulmonary cancer, compared with 19% in the middle emphysema category and 17% in the highest category. The corresponding numbers for those who received a lung cancer diagnosis were 2%, 3% and 11%, respectively.

Table 2 shows the distribution of the various non-pulmonary cancers. Although the incidence of the non-pulmonary cancers increased with increasing amount of emphysema, the distribution of non-pulmonary cancer did not differ between the amounts of emphysema (Fisher's exact test p=0.26). Airway wall thickness at baseline was not related to either lung cancer or non-pulmonary cancer (tables 3 and 4).

The univariate hazard ratios showed that older age, pack years, COPD status and amount of emphysema at baseline were significantly related to both incidences of non-pulmonary cancer and lung cancer (table 3). The hazard ratio for lung cancer by percentage of predicted FEV_1 also reached a level of significance; the lower the percentage of predicted FEV_1, the higher the hazard ratio (table 3).

After adjusting for sex, age and smoking (*i.e.* ex-*versus* current smoking, pack years and age of onset of smoking), the baseline amount of emphysema was still a significant predictor of incidence of both non-pulmonary cancer and lung cancer (table 4).

TABLE 2 Distribution of non-pulmonary cancers by level of emphysema

Cancer type	ICD10	LAA <3%	LAA 3–10%	LAA ⩾10%
Subjects n		61	28	30
1) Lip, oral cavity, pharynx	C00-C14	1.6	3.6	3.3
2) Digestive organs	C15-C26	13.1	42.9	20.0
3) Respiratory system, not lung	C32+C45	3.3	0.0	0.0
4) Skin	C43-C44	8.2	3.6	16.7
5) Retroperitoneum, peritoneum	C48	1.6	0.0	0.0
6) Breast cancer	C50	16.4	7.1	6.7
7) Female genital organs	C51-C58	4.9	7.1	0.0
8) Male genital organs	C60-63	24.6	10.7	13.3
9) Urinary tract	C64-C68	8.2	14.3	20.0
10) Eye, brain, central nervous system	C69-C72	4.9	0.0	6.7
11) Thyroid, other endocrine gland	C73-C75	3.3	0.0	0.0
12) Unknown primary site	C76+C83	1.6	0.0	3.3
13) Bone marrow	C90-92+D46-47	8.2	10.7	10.0
Sum		100	100	100

Data are presented as %, unless otherwise indicated. LAA: low-attenuation area; ICD10: International Classification of Diseases 10th Revision.

TABLE 3 Unadjusted analyses of predictors for incidence of pulmonary and non-pulmonary cancer from baseline to December 2013

Characteristics	Pulmonary cancer	Non-pulmonary cancer
Male	1.18 (0.59–2.36)	1.3 (0.90–1.89)
Age	1.07*** (1.04–1.11)	1.07*** (1.05–1.10)
Current smoking	0.87 (0.44–1.72)	0.48*** (0.32–0.71)
Age of onset of smoking	0.98 (0.90–1.06)	1.01 (0.97–1.04)
Pack years	1.03*** (1.02–1.05)	1.01 (1.00–1.02)
COPD cases *versus* controls	9.83*** (3.46–27.93)	1.45* (1.01–2.08)
FEV_1#	0.96*** (0.95–0.98)	1 (0.99–1.00)
Emphysema categories		
LAA <3%	Ref.	Ref.
LAA 3–10%	2.32 (0.78–6.93)	1.92** (1.22–3.01)
LAA ⩾10%	9.56*** (4.34–21.05)	2.18*** (1.41–3.39)
AWT-Pi10	0.82 (0.29–2.34)	1.04 (0.59–1.82)
Emphysema per 10% increase	1.95*** (1.58–2.41)	1.24* (1.05–1.46)

Data are presented as hazard ratio (95% CI). COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; LAA: low-attenuation area; AWT-Pi10: airway wall thickness (square root of wall area for airway with internal perimeter of 10 mm). #: percentage of predicted post-bronchodilator FEV_1. *: p<0.05; **: p<0.01; ***: p<0.001.

Finally, we added the *a priori* determined interaction terms to the equation. None of them reached the level of significance. We also repeated the analyses removing those patients with severe GOLD stages (stages C and D). The coefficients remained unchanged, indicating that the amount of emphysema was also related to an increased risk of lung cancer in the healthier part of the population (those with non-COPD and COPD stage A and B, results not shown).

We found no relationship between the location of emphysema in the lung and the location of the cancer. Nor did we find any relationship between emphysema and stage/metastasis in lung cancers, or between emphysema and the histological subtype of lung cancer (results not shown).

Discussion

The main findings of this prospective community-based study in subjects with and without COPD were as follows: 1) an increased amount of emphysema predicted an increased risk of non-pulmonary cancer, as well as lung cancer; and 2) airway wall thickness was related to neither lung cancer nor non-pulmonary cancer.

To our knowledge, this is the first study to show that emphysema predicts cancer outside the lungs. We observed that emphysema was a predictor of non-pulmonary cancer after adjusting for sex, age and smoking.

Several mechanisms may explain the association between emphysema and non-pulmonary cancer. First, COPD, with emphysema as a phenotype, is regarded as a systemic disease with one in six having chronic systemic inflammation [2]. Many inflammatory signalling pathways are activated in several types of cancer, linking chronic inflammation to tumour genesis [20]. Many inflammatory mediators, including cytokines,

TABLE 4 Associations of emphysema (and airway wall thickness) with incidence of pulmonary and non-pulmonary cancer from baseline to December 2013

	Pulmonary cancer	Non-pulmonary cancer
Emphysema per 10% increase	1.41* (1.00–1.97)	1.13 (0.89–1.44)
Emphysema categories		
LAA <3%	Ref.	Ref.
LAA 3–10%	1.21 (0.37–9.98)	1.55 (0.93–2.57)
LAA ⩾10%	3.33* (1.04–10.61)	2.10* (1.14–3.87)
AWT-Pi10	0.39 (0.12–1.29)	0.82 (0.42–1.59)

Data are presented as hazard ratio (95% CI). Adjusted for sex, age, percentage of predicted forced expiratory volume in 1 s, pack years, smoking status and age of onset of smoking. LAA: low-attenuation area; AWT-Pi10: airway wall thickness (square root of wall area for airway with internal perimeter of 10 mm). *: p<0.05.

chemokines, free radicals, growth factors and enzymes like matrix metalloproteinases may act to create a favourable microenvironment for the development of tumours [20]. Several of the signalling molecules mentioned above might be elevated in patients with COPD [2, 21]. Second, common genetic and epigenetic factors might also be responsible for both emphysema and non-pulmonary cancer [1]. Examples of such genes are those that code for telomerase reverse transcriptase (*TERT*) and NF-κB [22, 23]. Third, emphysema has been considered a marker of accelerated ageing in COPD [24]. Hence, emphysema might be an indicator of senescence of the lungs in the same way that muscle wasting and osteoporosis in COPD might be indicators of senescence in other organ systems. Accelerated ageing is related to increased risk of cancer development [25]. Consequently, both emphysema and increased risk of cancer could be part of an accelerated ageing process in patients with COPD. Finally, there could be other environmental risk factors for both emphysema and malignancies. An example is asbestos exposure, which can cause emphysema [26] and both pulmonary and non-pulmonary malignancies, at least in heavily exposed workers [27].

We also observed a relationship between quantitatively assessed emphysema and the risk of lung cancer. This is in line with previous studies using qualitative CT assessments [2–6], whereas studies using quantitative scoring have provided contradictory findings [7–9, 28]. Why did we find a positive emphysema–lung cancer correlation while other quantitative studies have failed to do so? The other quantitative studies were nested case–control studies sampled from lung cancer screening trials, whereas the present study was a community-based cohort of ever-smokers followed for 10 years. It might be that lung cancer screening trials do not represent the population with emphysema in general [3]. Even though the authors using qualitative assessments often state that the CT readers were unaware of the lung cancer diagnosis, it is possible that other radiographic characteristics, such as nodules, might have biased the readers' assessments of emphysema [3]. Our study using quantitative emphysema assessment is a strong argument for a true increased risk of lung cancer in those with emphysema. We observed a dose–response relationship between emphysema and lung cancer, which further strengthens this argument.

Several mechanisms may explain the association between emphysema and lung cancer, most of them being the same as stated for the association between emphysema and non-pulmonary cancer. These mechanisms include smoking as a prevalent risk factor for both emphysema and lung cancer through chronic inflammation and enzymatic imbalance. Emphysema may also cause scarring and repair processes that can lead to lung cancer. Finally, impaired mucociliary clearance in emphysema may cause an accumulation of carcinogens in the lungs.

We did not observe any relationship between airway wall thickness in terms of Pi10 and incidence of lung cancer. This is in line with the findings of a nested case–control study that included 117 matched pairs of lung cancer cases and controls sampled from a screening trial [7]. Other reports from our study population have shown that increased Pi10 is an independent predictor of respiratory symptoms, and also of respiratory mortality in those with severe emphysema [19, 29]. Airway wall thickening in COPD corresponds with chronic inflammation, but also with structural modifications including hypertrophy and hyperplasia of parietal glands, enlargement of goblet cells and mucus production [30, 31]. It may be hard to determine if airway wall thickness as measured by Pi10 reflects active, stable or burned out disease [32]. Hence, the lack of an association between Pi10 and lung cancer may indicate that Pi10 is an unspecific measure of airway inflammation.

The present study has several important strengths. First, it is a large single-centre study, which allows for extensive adjustment for important confounders. The participants were not sampled from a cancer screening trial, but from a community-based sample followed for more than 8000 person years. Second, all the CT scans were performed using the same scanner and were quantitatively interpreted. Third, this is a prospective study in which all the lung cancers and non-pulmonary cancers were incident cases, diagnosed after the CT scanning. Fourth, the cancer diagnoses were taken from the Norwegian Cancer Register with a close to 100% inclusion rate and histologically verified cancer diagnosis [10]. Finally, we also adjusted for the percentage of predicted FEV_1 without this affecting the overall findings of the study. However, it could be argued that FEV_1 is not a potential confounder in the emphysema–cancer relationship because FEV_1 does not cause emphysema but rather is at least partly an effect of emphysema.

Some limitations should also be acknowledged. First, the study was primarily designed to examine COPD patients. Thus, the number of incident cancer cases was small. Further, the design did not allow for a correlation assessment of the amount of emphysema *versus* the type of lung cancer. Second, it could be argued that COPD is mainly a distal airway disease whereas the Pi10 measurements reflect central airway conditions. However, findings in the central airways correspond to those in the distal airways [33]. Third, 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 [34].

Moreover, other studies have shown that limited CT scans can produce values of overall emphysema that are comparable to complete volumetric CT scans [35]. Fourth, the study did not include never-smokers, which prevents us from generalising the results to never-smokers. However, smokers with as low a smoking consumption as 2.5 pack years were included. Fifth, the CT assessment did not include the type of emphysema. Sixth, the study did not include GOLD stage I, which in some studies has shown to have the highest incidence of lung cancer [36].

It is well known that COPD patients have an increased risk of lung cancer. This study indicates that emphysema should be taken into account when evaluating those at high risk for not only lung cancer, but also non-pulmonary cancer. Further studies should be conducted to see if these patients could benefit from screening programmes.

In conclusion, this study offers a strong argument that emphysema is an independent risk factor for non-pulmonary cancer and lung cancer. Airway wall thickness in terms of Pi10 did not predict either non-pulmonary cancer or lung cancer.

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